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Microbiota: a novel regulator of pain

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Abstract

Among the various regulators of the nervous system, the gut microbiota has been recently described to have the potential to modulate neuronal cells activation. While bacteria-derived products can induce aversive responses and influence pain perception, recent work suggests that "abnormal" microbiota is associated with neurological diseases such as Alzheimer's, Parkinson's disease or autism spectrum disorder (ASD). Here we review how the gut microbiota modulates afferent sensory neurons function and pain, highlighting the role of the microbiota/gut/brain axis in the control of behaviors and neurological diseases. We outline the changes in gut microbiota, known as dysbiosis, and their influence on painful gastrointestinal disorders. Furthermore, both direct host/microbiota interaction that implicates activation of "pain-sensing" neurons by metabolites, or indirect communication via immune activation is discussed. Finally, treatment options targeting the gut microbiota, including pre- or probiotics, will be proposed. Further studies on microbiota/nervous system interaction should lead to the identification of novel microbial ligands and host receptor-targeted drugs, which could ultimately improve chronic pain management and well-being.

Keywords Microbiota · Visceral pain · Microbiota/gut/brain axis · Probiotic treatment

Abbreviations

ANS	Autonomic nervous system
ASD	Autistic spectrum disorder
CD	Crohn's disease
CGRP	Calcitonin gene-related peptide
CHS	Colonic hypersensitivity
CIPN	Chemotherapy-induced peripheral neuropathy
CNS	Central nervous system
CP	Chronic prostatitis
CPPS	Chronic pelvic pain syndrome
CpG	Cytosine guanosine
DRG	Dorsal root ganglion
EC	Enterochromaffin cells
EPM	Extracellular polymeric matrix
FD	Functional dyspepsia
FODMAPs	Fermentable oligo-, di-, monosaccharides and polyols
FMT	Fecal microbiota transplantation
FPR	Formyl peptide receptor
GABA	Gamma-amino butyric acid
GF	Germ-free
GPR41	G-coupled receptor 41
HDAc	Histone deacetylase
HPA	Hypothalamic/pituitary/adrenal
IC	Interstitial cystitis
IL	Interleukin
IBD	Inflammatory bowel disease
IBS	Irritable bowel syndrome
LPS	Lipopolysaccharide
Lypd8	Ly6/Plaur domain-containing 8
LTA	Lipoteichoic acid

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MAM	Microbial anti-inflammatory molecule
MAPKs	Mitogen-activated protein kinases
NF-κB	Nuclear factor-κB
NLR	NOD-like receptor
NOD	Nucleotide oligomerization domain receptor
PAMP	Pathogen-associated molecular pattern
PGN	Peptidoglycan
PI-IBS	Post-infectious IBS
PRRs	Pattern recognition receptor
PSA	Polysaccharide A
SCFA	Short-chain fatty acid
TIR	Toll/interleukin-1 receptor
TLR	Toll-like receptor
TNF	Tumor necrosis factor
TRP	Transient receptor potential channel
TRPA1	Transient receptor potential ankyrin member 1
TRPM3	Transient receptor potential melastatin member 3
TRPM8	Transient receptor potential melastatin member 8
TRPV1	Transient receptor potential vanilloid member 1
TRPV4	Transient receptor potential vanilloid member 4
UC	Ulcerative colitis
5-HT	5-hydroxytryptamine or serotonin

Introduction

Pain, which affects millions of people worldwide, is difficult to treat and can affect mood, social and professional life. While acute pain can contribute to a defense mechanism against microbes, fungi or viruses, maladaptive changes in the nervous system can drive the transition to chronic persistent pain post-infection.

Bacteria, archaea, viruses, fungi, protozoa, and helminths that populate our bodies are a thriving dynamic population forming a symbiotic superorganism. Current estimates suggest that approximately ~ 10^{14} microbes live on or in the human body with the number of microbial cells outnumbering the human cells (Sender et al. 2016). The greatest density of microbes resides in our gastrointestinal tract, particularly the colon part, which has received attention. The recent surge of gut microbiome-related studies over the last decade results from the rapid advancement of culture-free, affordable DNA sequencing technologies to identify commensal species within a given microbial community as well as the increased accessibility to germ-free (GF) animals, predominantly mice, enabling us to shape and control microbial reconstitution (Lozupone et al. 2012). These studies have highlighted the microbiota/gut/brain as a central axis in the development of central nervous system (CNS) and revealed an unexpected role of the gut microbiota on many aspects of brain function (Cryan and Dinan 2012). Using GF mice, numerous studies have shown that these mice in adulthood have marked changes in neurotransmitter levels, plasticity-related proteins, increased stress response, changes in anxiety and social behavior and also in pain perception (Luczynski et al. 2017).

It is now widely described that interaction in the microbiota/gut/brain axis is bidirectional. Efferent nerves of the central nervous system (CNS) modulate the gastrointestinal tract including microbiota via the sympathetic and parasympathetic branches of the autonomic nervous system (ANS), as well as via the hypothalamic/pituitary/adrenal (HPA) axis (Crowell 2004). These pathways can influence the enteric microbiota indirectly by modifying its environment and directly via a large number of signaling molecules including immunoregulatory neuropeptides with antimicrobial properties (Mayer et al. 2015). Afferent GI nerves from the host detect quorum-sensing molecules produced by microbes to communicate with one another (Janssens et al. 2018). These molecules include short-chain saturated fatty acids (SCFA), metabolites of bile acids, and neuroactive substances such as gamma-aminobutyric acid (GABA), tryptophan precursors and metabolites, serotonin, and catecholamines. It also includes cytokines released during the immune response to microbes, which can specifically signal to the host via receptors on local epithelial and mesenchymal cells within the gut. These factors can also signal via neurocrine pathways (vagal and possibly spinal afferences) and endocrine mechanisms to target well beyond the gastrointestinal tract, including vagal afferents in the portal vein and receptors in the brain (Mayer et al. 2015). Some of these signaling mechanisms can occur in the presence of an intact epithelium but are likely enhanced and altered in the context of increased intestinal permeability induced by stress (Da Silva et al. 2014) or mucosal inflammation (Hsiao et al. 2013).

Alterations of the microbiota/gut/brain axis have been described in chronic intestinal pathologies such as irritable bowel syndrome (IBS) or inflammatory bowel disease (IBD). These intestinal pathologies are also associated with cognitive disorders, an anxio-depressive phenotype, stress but also, at the intestinal level, alterations of transit and permeability, inflammation, as well as an infectious etiology and dysbiosis (Ringel and Ringel-Kulka 2015). Accumulating work suggest indeed a dominant role of the intestinal microbiota in the appearance of these two types of pathologies. According to a recent study, intestinal dysbiosis is present in 73% of IBS patients, in 70% of IBD patients (naive treatment) and in 80% of patients with quiescent IBD compared to only 16% of healthy subjects (Casén et al. 2015). Abdominal pain associated with colonic hypersensitivity (CHS) is also an important symptom of IBD and IBS patients, strongly affecting the patients' quality of life (Piche

et al. 2010). One hypothesis about chronic abdominal pain is that intestinal dysbiosis could significantly contribute to the initiation and the maintenance of the observed symptom.

In addition to intestinal disorders, increasing evidence suggests a correlation between dysbiosis and neurological diseases like Parkinson's or Alzheimer's disease (Dutta et al. 2019; Fox et al. 2019; Rueda-Ruzafa et al. 2019). Recent works indicate that specific microbial metabolites drive neuroinflammatory processes, as well as motor and cognitive deficits in mouse models of Alzheimer's or Parkinson's disease, illustrating the impact of microbiota on brain functions. This could provide exciting research interests in the field of microbiota/gut/brain axis and neurological diseases. Nevertheless, in contrast to chronic intestinal pathologies, only a very few studies seem to link gut dysbiosis and bacteria-derived metabolites to pathological pain including neurological diseases without a priori colonic involvement, like autism.

In this review, we will focus on preclinical and clinical studies highlighting an impact of microbiota on pain perception in a disease context. On the other hand, we will detail by which pathogen-associated metabolite, the microbiota may activate nociceptors and so participate in pain pathway activation.

Modification in microbiota associated with chronic pain

Gut microbiota

Gut microbiota regulates many aspects of host physiology including metabolism, immune system maturation, brain development and behavior (Sekirov et al. 2010). Shifts in intestinal microbial composition (dysbiosis) and function may lead to the development of diseases. Among them are gastrointestinal disorders such as IBS and IBD, but also extra-intestinal pathologies such as fibromyalgia, cancers, metabolic syndrome, rheumatic diseases, allergic and atopic disease, heart disease and neuropsychiatric diseases (Ahmadmehrabi and Tang 2017; Cryan and Dinan 2012; Festi et al. 2014; Sekirov et al. 2010; Van de Wiele et al. 2016). Many of these studies have focused on the pathological mechanisms associated with dysbiosis. We will present the current state of knowledge of the functional relationship between microbes and pain.

Visceral pain

In the last decade, preclinical models have been used to determine the involvement of the intestinal microbiota in visceral pain. The application of a psychological or physical stress either chronic or in early life is a key factor in the development of visceral pain. Several studies have shown that GF mice (raised in a sterile environment from birth) exhibit visceral hypersensitivity accompanied by an increase in Toll-like receptor expression (TLR1-9) and cytokine levels such as interleukin (IL) 6, IL-10 or tumor necrosis factor (TNF)-α in spinal cord. However, these changes were normalized by postnatal colonization with conventional microbiota (Luczynski et al. 2017; O'Mahony et al. 2013; Sudo 2012; Sudo et al. 2004). These findings indicate that commensal intestinal microbiota is necessary for balancing the excitability of colonic sensory neurons.

Likewise, antibiotics administered in early life induce visceral hypersensitivity in adulthood. This is associated with alterations in ion channels and receptors such as decrease in the transient receptor potential vanilloid member 1 (TRPV1), the alpha-2A adrenergic receptor, and cholecystokinin B receptor in the spinal cord (O'Mahony et al. 2014). However, in adult, antibiotic effects are controversial. Studies have shown that antibiotic treatment decreased visceral hypersensitivity induced by intraperitoneal acetic acid injection or intracolonic capsaicin infusion in mice, whereas naive rats displayed hyposensitivity (Aguilera et al. 2015; Hoban et al. 2016). Another study showed that antibiotic treatment induced visceral hypersensitivity in association with local immune response (Verdú et al. 2006).

Strikingly, visceral hypersensitivity can be transferred in GF rats by fecal microbiota transplantation (FMT) from IBS patients. Although colorectal compliance, epithelial paracellular permeability and density of colonic mucosal mast cells remained normal, recipient mice exhibited visceral hypersensitivity to colorectal distension and increased hydrogen sulfide production known to promote nociceptive behavior following colorectal infusion (Crouzet et al. 2013; Matsunami et al. 2009).

Various studies demonstrate the efficacy of probiotic administration on visceral hypersensitivity. In fact, *Lactobacillus paracasei* NCC2461 in mice, *Faecalibacterium prausnitzii* and the probiotic mix VSL#3 in rats decreased the maternal separation stress-induced visceral hypersensitivity (Distrutti et al. 2013; Eutamene et al. 2007; Miquel et al. 2016; O'Mahony et al. 2012). Similarly, in a restraint stress-induced visceral hypersensitivity, *Bifidobacterium lactis* CNCM I-2494 attenuated the nociceptive response (Agostini et al. 2012). VSL#3 also prevented inflammation-induced visceral hypersensitivity after intracolonic instillation of 4% acetic acid (Dai et al. 2012). On the other hand, *Bifidobacterium infantis* 35624 ameliorated visceral hypersensitivity in the trinitrobenzene sulphonic acid-induced (TNBS) model of colitis in rats and blunted nociceptive responses as described for *Lactobacillus paracasei* NCC2461 and *Lactobacillus reuteri* (Johnson et al. 2011; Kamiya et al. 2006; McKernan et al. 2010; Verdú et al. 2006).

Irritable bowel syndrome (IBS) Irritable bowel syndrome (IBS), the leading cause of consultation in gastroenterology, is an intestinal functional disease with a global prevalence of 11.2% in 2016, higher in Western countries (Enck et al. 2016). This intestinal disorder is characterized by frequent abdominal pain associated with changes in stool consistency and frequency, in the absence of changes in bowel structure. IBS is a multifactorial pathology whose pathogenesis is not yet fully understood. Several types of functional alterations in visceral sensitivity, brain function, intestinal motility or secretory function have been reported in IBS patients. The multifactorial etiology of IBS makes it impossible to envision the development of a single treatment applicable to all patients. The current treatments are symptomatic and they will target, according to the patients, the modifications of the transit, the bloating and/or the pain. The usual therapy also varies according to the severity of the syndrome but generally remains largely insufficient regarding the management of pain and associated CHS.

Intestinal dysbiosis associated with IBS: The concept that alterations in the gut microbiota composition might be relevant to IBS arose from observations that symptoms of IBS often developed after an infection (Lee et al. 2017) and some data suggest that the colonic microbiome composition and function is altered in IBS patients in comparison with healthy controls (Enck and Mazurak 2018).

The role of certain pathogens in the development of post-infectious (PI) IBS is now well established. In fact, more than 50 years ago, infectious enteritis was identified as a risk factor for IBS. The prevalence of PI-IBS varies between 4 and 36% and the symptoms especially visceral pain may persist up to 10 years after gastrointestinal infection (Klem et al. 2017). Bacteria such as *Shigella spp*., pathogenic *Escherichia coli*, *Salmonella* and *Campylobacter jejuni*, viral (Norovirus) enteritis, or protozoa parasite as *Giardia duodenalis* or potentially *Blastocystis* have been found to be linked to PI-IBS (Cremon et al. 2014; Kowalcyk et al. 2014; Nielsen et al. 2014; Nourrisson et al. 2014; Porter et al. 2012; Rostami et al. 2017; Tan 2008; Wensaas et al. 2012; Youn et al. 2016; Zanini et al. 2012). In a recent meta-analysis, the rate after infectious enteritis was higher with parasite (+40%) than bacterial (+14%) or viral infections (+4%) (Klem et al. 2017). Virulence of the pathogen but also the duration of infection is also a risk factor in PI-IBS (Lee et al. 2017).

Various studies described intestinal dysbiosis in IBS patients. While data are heterogeneous, the gut microbiota appears to play an important role in IBS pathogenesis. The modulation of the ratio *Firmicutes*/*Bacteroidetes* is an indicator of changes in the microbiota composition. In the literature, studies described an increase or a decrease in this ratio in IBS patients (Jalanka-Tuovinen et al. 2014; Jeffery et al. 2012; Pozuelo et al. 2015; Tana et al. 2010; Tap et al. 2017). The controversial data may be explained by the primers used for the amplification of a variable region of the 16S rRNA gene, the DNA extraction method, the small number of patients with IBS included in the study, the subtype of IBS diagnosed or the severity of the pathology. Globally, studies have shown an increase in the relative abundance of pro-inflammatory bacteria including the family *Enterobacteriaceae* and a reduction in the relative abundance of the genera *Lactobacillus* and *Bifidobacterium* (Duboc et al. 2012; Kerckhoffs et al. 2009; Parkes et al. 2012; Zhuang et al. 2017). Interestingly, the species *Faecalibacterium prausnitzii* and the genus *Bifidobacterium*, the families of *Ruminococcaceae* and *Erysipelotrichaceae,* and the order *Clostridiales* are SCFA-producing bacteria known to be involved in intestinal homeostasis (Rooks et al. 2014). Various studies have shown a reduction in the relative abundance of these bacteria in IBS patients (Lyra et al. 2009; Pozuelo et al. 2015; Rigsbee et al. 2012; Saulnier et al. 2011; Tana et al. 2010; Zhuang et al. 2017). Moreover, studies shown modulation of the quantity of SCFAs in IBS patients (Farup et al. 2016; Gargari et al. 2018; Treem et al. 1996), but the results are sometimes contradictory (Tana et al. 2010). While some studies described a reduction in SCFA levels, an increase in these levels was observed correlated with an increase in some SCFA-producing bacteria such as *Roseburia*, *Blautia* and *Veillonella* (Rajilić-Stojanović and de Vos 2014).

In addition, changes in the relative abundance of other type of bacterial were demonstrated in other studies. Increase in the relative abundance of *Ruminococcus* including *R. gnavus* and *R torques* which are able to degrade mucus, *Bacteroides* or *Streptococcus* can lead to IL-6 production (Jalanka-Tuovinen et al. 2014; Jeffery et al. 2012; Lyra et al. 2009; Malinen et al. 2005; Parkes et al. 2012; Ponnusamy et al. 2011; Rigsbee et al. 2012; Ringel and Ringel-Kulka 2015; Saulnier et al. 2011; Tana et al. 2010). More recently, an increase in the relative abundance of the genus *Prevotella* has been associated with the development of IBS (Su et al. 2018). Interestingly, the relative abundance of sulfate-reducing bacteria is enhanced in IBS patients (Crouzet et al. 2013). In addition, methane has been associated with the development of IBS. The production of methane is limited to the reign of the archaea, particularly *Methanobacteriales* in humans and the increase in methane levels in patients with IBS (Kim et al. 2012; Pimentel et al. 2006; Tap et al. 2017) is characterized by the presence of *Methanobacteriales* associated with increased level of *Clostridiales* resulting in a slower transit (Falony et al. 2016; Jahng et al. 2012; Pimentel et al. 2006; Tap et al. 2017; Vandeputte et al. 2016). Strikingly, the severity of the symptoms is positively correlated with the presence of these archaea and an increase in the abundance of bacteria belonging to the order of *Clostridiales* or genus *Prevotella* (Rodiño-Janeiro et al. 2018).

More recently, fecal fungi were examined in IBS patients with or without visceral hypersensitivity compared to healthy individuals (Botschuijver et al. 2017). The fecal mycobiota of healthy individuals consists of 57% of the species *Saccharomyces cerevisiae* and *Candida albicans*. This percentage rises to 76% in hypersensitive and to 83% in normal-sensitive patients, indicating that IBS patient present a significant increase in the abundance of these two strains of yeast regardless of their visceral sensitivity. In addition, the fungal diversity is decreased among IBS patients compared to control subjects. In this study, animal experiments revealed that CHS induced during neonatal stress could be reduced by the use of antifungals (Botschuijver et al. 2017). These results therefore suggest the contribution of certain fungal communities in eliciting IBS symptoms such as CHS associated with chronic abdominal pain. However, further studies are needed to confirm these results and also evaluate the possible disturbances of the mycobiota according to the different subtypes of IBS.

Treatment by modulation of the microbiota composition: Data from previous studies suggest that alterations in the gut microbiota composition and function may induce or exacerbate existing symptoms. This then raises the question of whether antibiotics, or other related interventions, can be used to modulate the gut microbiome and thus improve IBS symptoms. A recent meta-analysis identified 4017 citations (Ford et al. 2018). Authors showed that data for prebiotics and symbiotic studies were controversial. With probiotics, some combinations, or specific species and strains appeared to have beneficial effects on abdominal pain (Didari et al. 2015; Ford et al. 2018; Rondanelli et al. 2017), but the heterogeneity of studies by the strain or the quantity used and duration of the treatment does not allow drawing definite conclusions about their efficiency. Moreover, host and microbiome features contribute to the efficiency of probiotics and may explain differences between studies (Zmora et al. 2018).

Moreover, few trials using antibiotics like rifaximin showed modest efficiency in improving symptoms. Nevertheless, there is a growing interest in fecal microbiota transplantation (FMT) therapy for several gastrointestinal disorders. While data for FMT in IBS patients were sparse (Xu et al. 2019), FMT therapy was successful in treating *Clostridium difficile* infection, suggesting that future work is warranted to demonstrate the therapeutic value of microbiota reconstitution.

The majority of IBS patients had worsening symptoms after eating certain foods that were rich in carbohydrates, lipids and had a high calorie count (Böhn et al. 2013; Le Nevé et al. 2013; Posserud et al. 2013). The first recommendations are to eat "healthier", meaning to avoid or limit the consumption of alcohol, caffeine, spicy or high-fat foods, but also to limit the size and number of meals (Simrén and Tack 2018). When the symptoms are not reduced with this "healthier" diet, it is then proposed to follow a low-fermentable oligo-, di-, monosaccharides and polyols (FODMAPs) diet (Simrén and Tack 2018). Clinical studies reported a reduction in symptoms in IBS patients with a diet depleted in FODMAPs (Halmos et al. 2014; Pourmand and Esmaillzadeh, 2017; Shepherd et al. 2008; Staudacher et al. 2017; Zahedi et al. 2018). So far, most of the studies were conducted over short periods (up to 4 weeks) but a low FODMAPs diet rather than a complete elimination may be effective in the longer-term treatment (O'Keeffe et al. 2018; Whelan et al. 2018). In addition, a depleted regime in FODMAPs may favor changes in the composition of the intestinal microbiota (Schumann et al. 2018). Thus, this scheme can be used in combination with probiotics to preserve gut microbiota and prevent in particular the reduction in the abundance of the genus *Bifidobacterium*, characteristic of IBS patients (Staudacher et al. 2017).

A gluten-free diet has also been mentioned in the treatment of IBS symptoms (Biesiekierski et al. 2011). Evidence is emerging about the decrease in activation of immune system in a gluten-free diet (Uhde et al. 2016). However, no direct link has been established between the development of symptoms associated with IBS and gluten.

Inflammatory bowel disease (IBD) Pain is one of the most common causes of disability and impaired quality of life in IBD, which regroups Crohn's disease (CD) and ulcerative colitis (UC) (Lönnfors et al. 2014). IBD has a prevalence of 322 cases per 100,000 people worldwide and 505 cases per 100,000 people in Europe. They are characterized by acute intestinal inflammatory flares of extremely variable duration and frequency, interspersed with more or less long periods of remission, spontaneous or under the influence of treatments. However, despite successful treatment of active disease, the symptoms of abdominal pain are out of proportion with the observed degree of inflammation (Long and Drossman 2010). These symptoms, known as IBS-like symptoms, are present in approximately 40% of IBD patients with a higher prevalence in CD than in UC patients (Halpin and Ford 2012). These pathologies present a multifactorial and complex etiology comprising immune system, microbiota and environmental factors on genetically susceptible individuals (Wallace et al. 2014). Indeed, genetic susceptibility may lead to an excessive immunological response to the gut microbiota or an imbalance in the microbiota composition resulting in environmental stress that may trigger a pathological response from the immune system (Strober et al. 2007).

Intestinal dysbiosis associated with IBD: Clinical studies have shown potential imbalance of the gut microbiota in IBD patients, with an overall loss of bacterial richness, a decrease of *Firmicutes* and an increase of *Proteobacteria* (Baumgart

et al. 2007; Frank et al. 2007; Manichanh et al. 2006; Ott et al. 2004; Sokol et al. 2006). However, like for IBS, these studies varied in their design resulting in spare results. A recent meta-analysis described a role of the gut microbiota in the activity of IBD. Indeed, compared to patients in remission, active IBD had lower abundance of *Clostridium coccoides, F. prausnitzii* and *Bifidobacterium*. Subgroup analyses showed a difference in all four bacteria between patients with UC classified as active or in remission. Patients with active CD had fewer *C. leptum*, *F. prausnitzii* and *Bifidobacterium*, but not *C. coccoides.*

Like with IBS patients, IBD patients display fungal dysbiosis characterized by an increased *Basidiomycota/Ascomycota* ratio, a decreased proportion of *Saccharomyces cerevisiae* and an increased proportion of *Candida albicans* compared with healthy control (Chehoud et al. 2015; Iliev et al. 2012; Sokol et al. 2017). Authors suggested that the inflammatory environment of CD favors the expansion of fungi over bacteria. However, studies of the mucosa-associated fungal composition have yielded similar variable results (Mukhopadhya et al. 2015; Ott et al. 2008).

Treatment by modulation of the microbiota composition: While the anti-inflammatory effect of microbiota manipulation was largely studied, only few studies focused on its analgesic effect. One study reported improvement of abdominal pain by antibiotics (Castiglione et al. 2003), but microbiota composition has not been studied.

Fermentable polysaccharide supplement known to have positive prebiotic properties was given to participants. Reduced abdominal pain was reported with tolerance, but disease status of patients was not reported. In other study, abdominal pain was reduced in CD patients after the consumption of used kefir, a source of carbonated and fermented milk product, containing lactic acid bacteria (Yilmaz et al. 2019).

The low FODMAPs diet has an important role in IBS management and so it has received considerable interest in its application to those with IBD. A recent meta-analysis support that a low FODMAPs diet is beneficial for reducing gastrointestinal symptoms such as abdominal pain in patients with quiescent IBD (Zhan et al. 2018).

Other pathologies associated with painful gastrointestinal disorders *Functional dyspepsia*: Functional dyspepsia (FD) is characterized by troublesome early satiety, fullness, or epigastric pain or burning. It can easily be overlooked as the symptoms overlap with gastro-esophageal reflux disease and IBS (Talley 2017). The pathophysiology of functional dyspepsia is not completely understood. As described for IBS, post-infectious gastroenteritis was recently identified as a risk factor for FD (Talley and Ford 2016). It has been hypothesized that the site of infection determines the symptom (Talley 2017). Indeed, infection in the small bowel may lead to intestinal hypersensitivity-related FD, while colon infection may lead to IBS (Spiller et al. 2010).

Chronic infection is also a risk factor for FD. Meta-analyses of randomized controlled trials established that *H. pylori* eradication had beneficial effects in controlling the symptoms of functional dyspepsia (Du et al. 2016; Suzuki and Moayyedi 2013). There is evidence that the duodenal microbiome is altered in FD and antibiotic therapy may reduce the symptoms (Igarashi et al. 2017). Rifaximin appears effective in FD but the effect on composition of the intestinal microbiota was not discussed (Tan et al. 2017; Yoon et al. 2018). Probiotics can also treat FD through the normalization of microbiota (Igarashi et al. 2017; Nakae et al. 2016; Takagi et al. 2016).

Infantile colic: Infantile colic is a behavioral syndrome characterized by excessive and inconsolable crying without identifiable cause during the 1st month of life (Daelemans et al. 2018). There is accumulating evidence that the intestinal microbiota in colicky infants differs from healthy controls. In some studies, intestinal microbiota of colicky infants is characterized by decrease in bacterial richness and decrease in the genera *Lactobacillus* and *Bifidobacterium*, while Gram-negative bacteria are increased (Savino et al. 2004; de Weerth et al. 2013). Luminal contents from colicky infants lead to visceral hypersensitivity in mice compared with non-colicky infants (Eutamène et al. 2017). While it is challenging to assess pain in infants, one study reported that manipulation of microbiota using probiotic or prebiotic reduced crying-associated pain (Pärtty et al. 2013; Szajewska and Dryl 2016).

Colonic diverticulosis: Colonic diverticulosis is characterized by protrusions of the mucosa through weak areas of the colonic musculature. This disease occurs in up to one-third of people over the age of 60 years and in most cases does not generate disabling symptoms (Stollman and Raskin 2004). However, in 10–25% of subjects, colonic diverticula are associated with abdominal pain and changes in bowel habit.

Alterations in the gut microbiota composition have been proposed as a potential etiological factor involved in the pathogenesis of diverticular disease and diverticulitis (Choung et al. 2011). While few studies have found a link between gut microbiota and symptoms, Barbara et al. showed that symptomatic patients displayed depletion of beneficial bacteria such as *Clostridium* cluster IV, *Clostridium* cluster IX, *Fusobacterium*, and *Lactobacillaceae* compared with asymptomatic patients (Barbara et al. 2017). Moreover, a recent study reported that abdominal pain was strongly correlated with fecal dysbiosis (Kvasnovsky et al. 2018).

Autism: Autism is a neurodevelopmental disorder characterized by impaired social interaction, verbal and non-verbal communication, and repetitive behavior (Lai et al. 2014).

In addition to cognitive aspects, autistic spectrum disorder (ASD) individuals can suffer from gastrointestinal problems such as abdominal discomfort, pain and gas distension (Holingue et al. 2018). The cause of gastrointestinal dysfunction in the ASD population is unclear. Altered microbiome–gut–brain pathways have been reported in ASD and may contribute to symptoms by changing microbiota composition. Moreover, some studies have reported higher oral antibiotic use in ASD children than typical children (Konstantareas and Homatidis 1987; Niehus and Lord 2006). Administration of antibiotics may disrupt intestinal microbiota and lead to gastrointestinal dysfunction commonly reported in ASD populations. Differences in the microbiota composition have been reported in several studies (De Angelis et al. 2013; Finegold et al. 2010; Kang et al. 2013; Wang et al. 2013). In addition, Luna et al. identified distinctive mucosal microbial signatures in biopsies from ASD children with functional GI disorders (Luna et al. 2017).

Extra-intestinal pain: the chemotherapy-induced pain

Chemotherapeutic drugs induce peripheral neuropathy in 30% of patients under treatment (Seretny et al. 2014). Chemotherapy-induced peripheral neuropathy (CIPN) is characterized by pain lasting months to years, which prevent patients from receiving adequate chemotherapy dosages (Hershman et al. 2014). In recent studies, the involvement of the intestinal microbiota in the tumor-killing effect of chemotherapeutic drugs has been described (Viaud et al. 2013). However, the association between intestinal microbiota with the incidence and progression of CIPN has rarely been investigated. Shen et al. showed that oxaliplatin-induced mechanical hyperalgesia was reduced in both mice pretreated with antibiotics and germ-free mice (Shen et al. 2017). This protection was reversed after colonization in germ-free mice. Reciprocally, there is evidence that chemotherapy can change the composition of microbiota (Stojanovska et al. 2018).

Urinary microbiota

The urinary tract is not sterile and possesses a complex microbiota that is regulated by various factors. Dysbiosis in the lower urinary tract can cause symptoms of interstitial cystitis, urinary urge incontinence, and chronic prostatitis/chronic pelvic pain syndrome (Magistro 2019).

Chronic prostatitis/chronic pelvic pain syndrome

Chronic prostatitis (CP)/chronic pelvic pain syndrome (CPPS) are chronic conditions characterized by pain or discomfort with significant impact on quality of life (Krsmanovic et al. 2014). CP/CPPS patients display a higher bacterial richness accompanied by a higher abundance of *Clostridia* compared with healthy controls resulting in predicted perturbations in functional pathways such as sporulation chemotaxis and pyruvate metabolism (Shoskes and Macoska 2017). Moreover, the prevalence of fungi (*Candida* and *Saccharomyces* sp.) is significantly greater in women who report a flare compared to those who do not (Nickel et al. 2016). About the gut microbiota, the bacterial richness is decreased in CP/CPPS patients with a significant decrease in the abundance of *Prevotella* (Shoskes et al. 2016).

Interstitial cystitis

Interstitial cystitis (IC) is defined by chronic pain associated at least with one additional symptom such as worsening pain with bladder filling or urinary frequency. IC patients harbor differences in the composition of midstream urine but also in the gut microbiota composition. Urinary microbiota of IC patients is characterized by a decrease in the bacterial richness accompanied by a higher abundance of the bacterial genus *Lactobacillus* and a lower abundance of *Corynebacterium* (Abernethy et al. 2017; Nickel et al. 2019; Siddiqui et al. 2012). Studies also described an improvement of symptoms after the eradication of *Lactobacillus* in the IC urine (Darbro et al. 2009). These results suggest that *Lactobacillus* impacts symptom severity, but the role of this genus in IC has still not been determined. On the other hand, a study described a reduction in abundance of *E. sinensis, C. aerofaciens, F. prausnitzii, O. splanchnicus,* and *L. longoviformis* in the gut microbiota composition compared to healthy controls (Braundmeier-Fleming et al. 2016).

Interactions between nervous system and bacteria

Chronic pain is a maladaptive response of the nervous system to inflammation or injury. In fact, pain can be induced by bacterial infection resulting from the dynamic interactions established between pathogens and the host (White 2009). It is generally accepted that pain sensation is related to inflammation pathway. However, different pathways can be involved in the sensation of pain: on the one hand, it can be induced by the immune pathway after the recognition of pathogen-associated molecular pattern (PAMPs), on the other hand, a crosstalk between microbial agent and the nervous system can lead to pain sensitization. Nociceptors are specialized sensory neurons, which detect potentially damaging stimuli to protect the host by eliciting pain and aversive behaviors (Fig. 1). To achieve this, nociceptors that have cell soma in dorsal root ganglion (DRG) propagate action potentials from the periphery to the spinal cord where it is integrated and transmitted to the cerebral cortex. Five

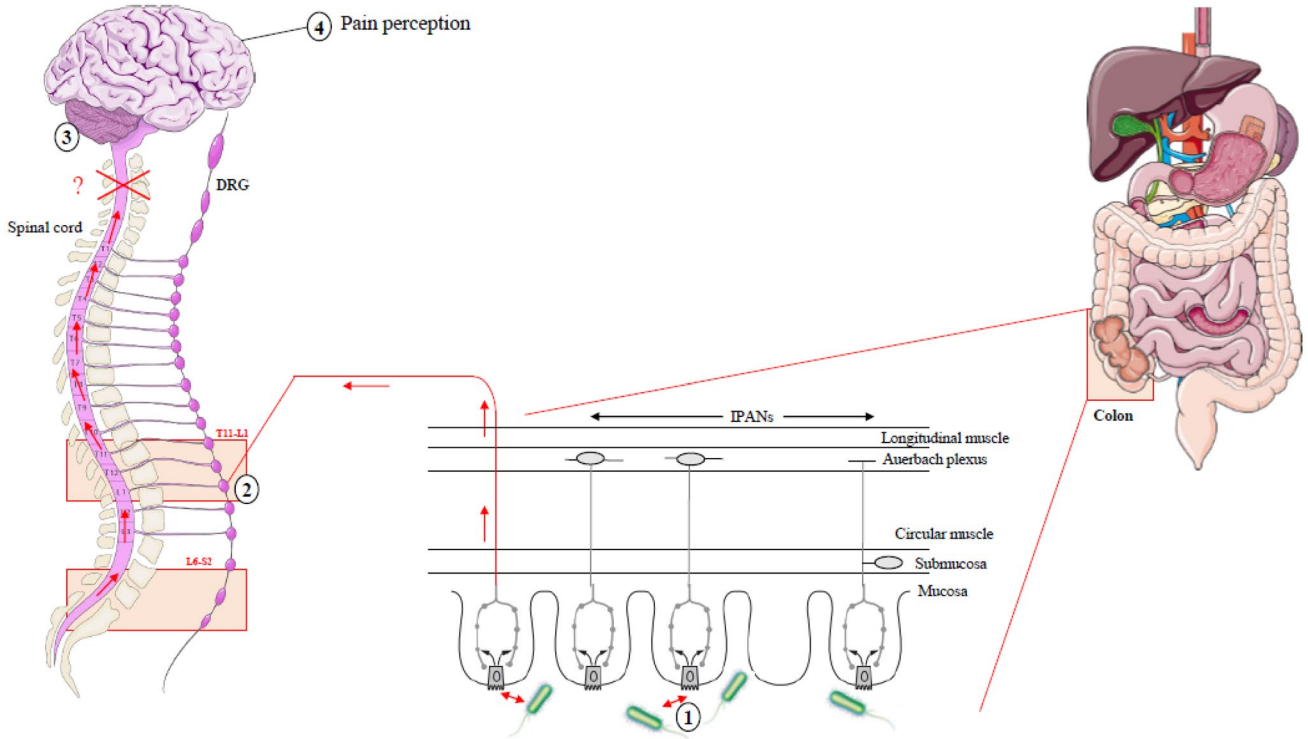

Fig. 1 Implication of gut microbiota in pain perception. (1) Gut microbiota can modulate pain perception via constitutive compounds and metabolites secreted. (2) Peripheral nociceptive signals are relayed by dorsal root ganglion (DRG). Axons of these neurons innervate multiple layers of the intestine and synapse with spinal cord. Message transmission is insured by spinal cord until the brain (3) where pain perception is transduced (4). *IPANs* intrinsic primary afferent neurons

years ago, it was found that bacterial products could activate nociceptors to cause pain. *Staphylococcus aureus* was shown to induce pain in mice by activating nociceptors via *N*-formyl peptides and the pore-forming toxin α-haemolysin (Chiu et al. 2013). In this respect, we can consider pain perception as a complex network between immune cells and the nervous system (Ren and Dubner 2010). Indeed, it has been found that receptors of immune cells and nervous cells are shared. In fact, TLR3, TLR7 and TLR9 are expressed by human dorsal root ganglia neurons and have both direct and indirect effects on pain initiation and regulation (Qi et al. 2011). However, when the communication between neurons, non-neuronal cells and immune cells is disrupted, it can result in a state of hypersensitivity.

Data from many clinical studies suggest that certain probiotic bacterial strains have the potential to modulate abdominal pain in case of IBS (Didari et al. 2015; Hungin et al. 2013; Moayyedi et al. 2010). It is the case of the strain *Escherichia coli* Nissle 1917 which is able to produce a lipopeptide C12AsnGABAOH and have analgesic properties. This compound is able to pass the epithelial barrier and to activate $GABA_B$ receptor (Pérez-Berezo et al. 2017). However, most of the time, data are contradictory and the mechanisms implied are not well understood. Indeed, it is difficult to compare data because of variable parameters (dose, mode of administration, probiotic strain, etc.) with different specific probiotics which have different effects on different patients. Therefore, probiotics constitute an interesting field of investigation, although it will be challenging in terms of study design. The comprehension of specificity of pathogen-derived molecules and the mechanisms of their detection by the nervous system is just at its beginning. Besides representing new insights of the study, a better comprehension of mechanisms involved in the modulation of pain perception may contribute to finding novel therapeutic strategies.

Indirect interaction between bacteria and the nervous system through immune activation

It is well accepted that pathogens can interact with sensory neurons through indirect mechanisms involving immune response. Detection of a pathogen and the initiation of a rapid defensive response constitute the principal challenge for the host (McCusker and Kelley 2013). Immune cells constitute the first line of host defense against microbial infection and the recognition by TLRs leads to the production of pro-inflammatory mediators (cytokines and chemokines)

that can finally induce sensory neurons activation and pain perception (Liu et al. 2012). TLRs are transmembrane glycoproteins belonging to PRRs (pattern recognition receptors) and consisting of two domains: an extracellular domain with leucin-rich repeat motifs and a toll/interleukin-1 receptor (TIR) signaling domain. These receptors belong to two different groups according to their localization in the cell: plasma membrane with TLR1, TLR2, TLR4-6 and TLR11 and endolysosomal membrane for the others (Kang et al. 2016). Activation of immune response can take place after recognition of PAMP localized at the surface of microorganisms. PAMPs are relatively conserved constituents of the cell wall of microorganisms including viral and bacterial nucleic acids, peptidoglycan (PGN), lipoteichoic acid (LTA), lipoproteins, lipopolysaccharides (LPS) (Medzhitov 2007) and flagellin as well as glucans, mannans, chitins and proteins derived from fungal cell wall (Kumar et al. 2009). The bacterial cell wall component PGN is a good example of PAMP which can be recognized by immune cells and initiate immune response. PGN, a peptide-crosslinked sugar polymer, constitutes the major element of the cell membrane both in Gram-positive and Gram-negative bacteria. The immune system can recognize both intact PGN and its fragments thanks to specific receptors belonging to TLR, TLR2 (Wolf and Underhill 2018), NOD1 (nucleotide oligomerization domain receptor 1) and NOD2 which trigger the production of pro-inflammatory cytokines and the recruitment of neutrophils cells to the site of infection (Inohara et al. 2005). TLR2 may recognize also LTAs present in Gram-positive bacteria (Wolf and Underhill 2018). The pathway implicated in the recognition of LPS by TLR is well understood. Indeed, LPS, a characteristic component of Gram-negative bacteria, is one of the best studied immunostimulatory components and is recognized by TLR4 (Lu et al. 2008). The recognition by TLRs induces activation of mitogen-activated protein kinases (MAPKs) and transcription factors such as nuclear factor-κB (NF-κB) contributing to the induction of type I interferon or proinflammatory cytokines and chemokines by macrophages (Kawai and Akira 2010). *N*-formyl peptides, motifs found on several bacteria represent another potential ligand that can induce immune response via their recognition by formyl peptide receptors (FPRs). In fact, FPRs are expressed by innate immune cells, and their activation lead to the recruitment of leukocytes and the production of pro-inflammatory cytokines to fight against microbial infection (Rooks and Garrett 2016). Finally, the innate immune system detects flagellated bacteria via TLR5. This activation leads to the release of antimicrobial peptides and secretion of chemokines that induce a recruitment of neutrophils. Flagellin is also recognized by NOD-like receptor family CARD domain-containing protein 4 (NLRC4). This receptor activates inflammasome complex causing the death of infected cells (Ley and Gewirtz 2016). This is a strategy to control the level of flagellated bacteria in the gut. To limit the access to the intestinal mucosa, colonic epithelial cells release Ly6/Plaur domain-containing 8 (Lypd8) that blocks motility of bacteria in the colon and constitute a mean to maintain microbiota homeostasis (Hsu et al. 2017; Ley and Gewirtz 2016; Okumura et al. 2016). Lypd8 is a highly glycosylated GPI-anchored protein highly and selectively expressed on the mucosal surface of the large intestine (Okumura and Takeda 2018). It was shown that Lypd8 inhibited motility of bacteria such as *Escherichia coli* and *Proteus mirabilis* and limited bacterial invasion of the colonic epithelia (Okumura et al. 2016). Many others compounds, produced by gut microbiota, can modulate pain perception via the modulation of the immune response. MAM (for Microbial Anti-inflammatory Molecule) is a protein (15KDa) which has been discovered in the supernatant of *Faecalibacterium prausnitzii*, a commensal bacterium deficient in Crohn disease, and is able to inhibit the NF-κB pathway in several intestinal cells lines (Quévrain et al. 2016). This strain stimulated lot of interest because several phylotypes are able to produce extracellular polymeric matrix (EPM) with immunomodulatory effects through TLR2 pathway and can modulate the release of IL-12 and IL-10 (Rossi et al. 2015). Many members of the gut microbiota produce metabolites that can modulate immune response among them, SCFAs or neurotransmitters. It is important to consider neuron–immune interactions in pain and inflammation. The immune system is a major player in pain by releasing mediators that can sensitize nociceptor function. This response is mediated by the activation of specific receptors and ion channels localized at the nerve terminal of the nociceptors. Resident and infiltrating immune cells like neutrophils, mastocytes and macrophages produce cytokines, lipids, proteases, histamine, serotonin (5-HT) and growth factors. The recognition of these pro-inflammatory molecules via specific mechanism of transduction that implicate TRPV1 and transient receptor potential ankyrin member 1 (TRPA1) channels, among other leads to neuron depolarization, action potential propagation along the afferent pain pathway (Pinho-Ribeiro et al. 2017).

Possible direct interaction between the gut microbiota and nociceptors

Interactions by constitutive elements

Many barrier tissues including the skin, gastrointestinal tract, genitourinary tract and respiratory tract are innervated by the somatosensory nervous system. Perception of pain is mediated by nociceptors but molecular and cellular mechanisms leading to the activation of nociceptors during infection are not well understood. Recent studies have shown that sensory neurons developed specific molecular mechanisms to detect pathogens, whether constitutive or

secreted molecules (Fig. 2 and Table 1). In addition to activating nociceptive signaling by cytokine release immune cells, Ochoa-Cortes et al. have shown that bacterial cell products have the potential to directly activate nociceptive signaling by altering the intrinsic excitability of nociceptive DRG neurons leading to modulate pain signaling (Ochoa-Cortes et al. 2010). In the same way as for immune pathway, pathogens are recognized by specific receptors called TLRs. TLR3, TLR4, TLR5, TLR7 can recognized double-stranded RNA, LPS, flagellin, single-stranded RNA, unmethylated cytosine-guanosine (CpG), respectively. Receptors belonging to the family of transient receptor potential channel (TRP) can also recognize LPS (Alpizar et al. 2017). Several immune receptors are also expressed on nociceptors. For example, the expression of TLR4 in adult DRG neurons in mouse has been demonstrated (Acosta and Davies 2008). In addition, Gram-negative bacteria have the ability to influence sensory neurons. In fact, LPS can directly activate sensory neurons and sensitize TRPV1-mediated capsaicin responses in trigeminal sensory neurons in vitro via TLR4 pathway (Diogenes et al. 2011; Ferraz et al. 2011). The interaction between LPS and TLR4 is well documented and might trigger intracellular signaling cascades in the nociceptors, leading to the sensitization of TRPV1. For example, *E. coli*-derived LPS activated TRPV1 channels in trigeminal neurons (Diogenes et al. 2011). Several studies have demonstrated the role of nociceptors in releasing pro-inflammatory neuropeptides to mediate neurogenic inflammatory responses (De Logu et al. 2018). Its implication in inflammatory hyperalgesia is mediated by the release of vasoactive neuropeptides such as calcitonin gene relative peptide (CGRP) and substance P that have powerful effects on immune cell recruitment and activation during infection. These findings are consistent with the hypothesis that bacteria can establish direct interactions with sensory neurons. TRPV1 constitute a potential therapeutic target for chronic visceral pain, because clinical studies have demonstrated upregulation of TRPV1 expression or increase of TRPV1

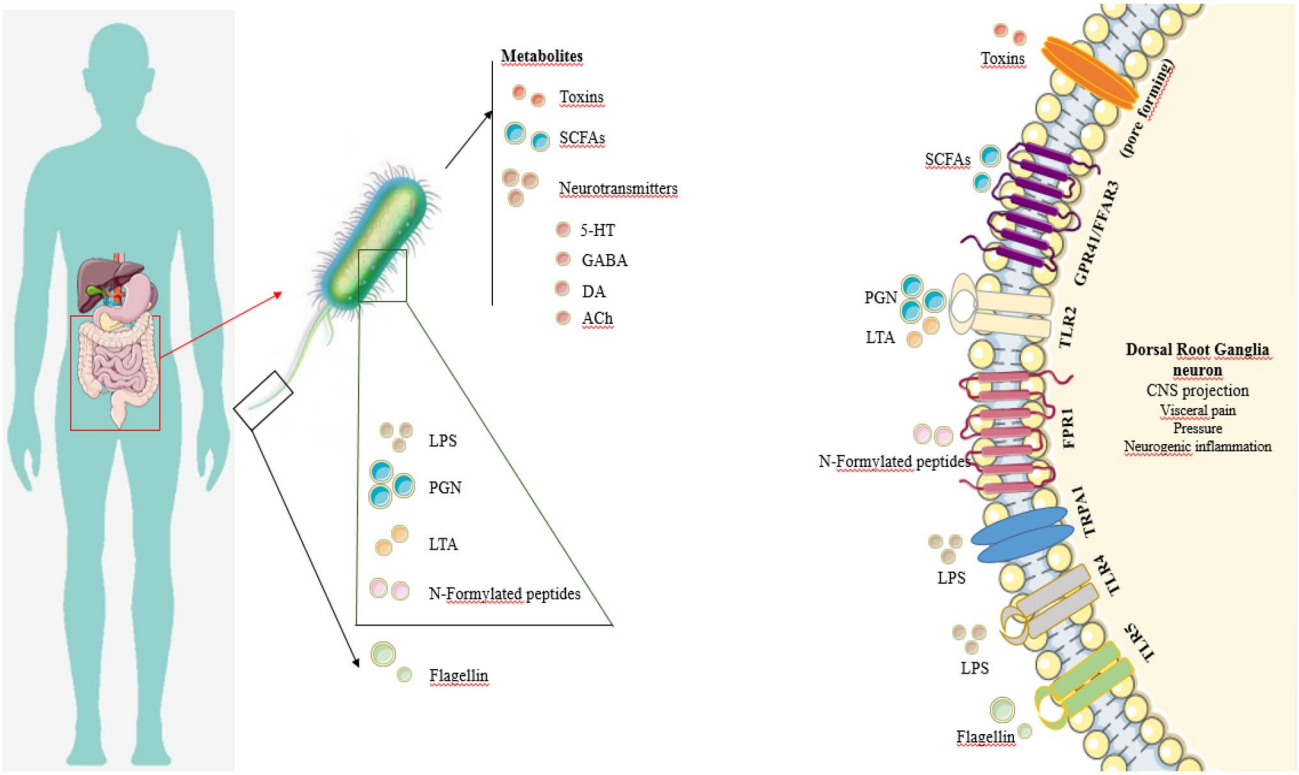

Fig. 2 Possible interaction between gut microbiota and sensory neurons via constitutive components or secreted metabolites. On one side, gut microbiota presents a large amount of constitutive elements, especially on bacterial membrane or secreted metabolites. On the other side, the expression of several specific receptors has been demonstrated and makes possible the potential direct interaction between bacteria and sensory neurons. For constitutive constituents, this is the case of TLR4 and TRP1, receptors that can recognized LPS, or FPR1 which can recognize N-formylated peptides, TLR5 implicated in the recognition of flagellin and TLR2 with PGN and LTA. Metabolites secreted by gut microbiota can also interact with others specific receptors. For example, SCFAs which can be recognized by GPR41/FFAR3. *LPS* lipopolysaccharide, *PGN* peptidoglycan, *LTA* lipoteichoic acids, *SCFAs* short-chain fatty acids, *GABA* gamma amino butyric acid, *TLR2* toll-like receptor 2, *TLR4* toll-like receptor 4, *FPR1* formyl peptide receptor 1, *GPR41* G-coupled receptor 41, *FFAR3* free fatty acid receptor 3, *DA* dopamine, *Ach* acetylcholine

Table 1 Several evidences that direct communication between bacteria and neurons is theoretically possible

Bacterial strain/bacterial component/metabolites	Molecular recognition/mechanisms	References
Evidences of direct interaction between bacteria and neurons		
Lipopolysaccharides	LPS sensitizes TRPV1 via activation of TLR4 in trigeminal sensory neurons	Diogenes et al. (2011)
	TRPA1 channels mediate acute neurogenic inflammation and pain produced by bacterial endotoxins. Neurogenic inflammation caused by LPS is dependent on TRPA1 channel activation	Meseguer et al. (2014)
	LPS activates TRPV1, TRPM3, TRPM8 in mouse dorsal root ganglia	Boonen et al. (2018)
	Lipopolysaccharides from *Porphyromonas gingivalis* sensitizes capsaicin-sensitive nociceptors	Ferraz et al. (2011)
Escherichia coli NLM28 lysate	*Escherichia coli* NLM28 lysate increased action potential discharge over 60% compared with control medium. Lysate activates afferent discharge from colonic mesenteric nerves. These data demonstrate that bacterial cell products can directly activate colonic DRG neurons leading to production of inflammatory cytokines by neurons and increase excitability	Ochoa-Cortes et al. (2010)
Toxins from *Staphylococcus aureus*	Nociceptor neurons showed calcium influx, action potential generation, and neuropeptide release in response to α-haemolysin toxin from *Staphylococcus aureus*. The toxin may directly depolarize neurons by forming pore and allowing cations to enter to cytoplasm. Toxin-induced nociceptor neurons release the immunomodulatory neuropeptide CGRP and reinforce local inflammatory response	Chiu et al. (2013)
Toxin from *Mycobacterium ulcerans*	Mycolactone elicits signaling through type 2 angiotensin II receptors and lead to potassium-dependent hyperpolarization of neurons, a direct nerve cell destruction leading to hypoesthesia	Marion et al. (2014)
N-formylated peptides of *Staphylococcus aureus*	*Staphylococcus aureus* induces calcium flux and action potentials in nociceptor neurons, in part via *N*-formylated peptides and the pore-forming toxin alpha-haemolysin	Chiu et al. (2013)
Lactobacillus rhamnosus LGG	Studies using the formyl peptide receptor 1 and two knockout mice revealed that effects of LGG on enteric neuronal signaling were largely mediated by FPR1, expressed on enteric neuronal cells	Chandrasekharan et al. (2019)
Polysaccharide A from *Bacteroides fragilis*	Application of PSA induces action potential in IPAN enteric sensory neurons in ex vivo intestinal preparations	Mao et al. (2013)
Amuc_1100 from *Akkermansia muciniphila*	Amuc_1100 can interact with cells expressing TLR2	Plovier et al. (2017)
Serine proteases from *Faecalibacterium prausnitzii*	Serine protease can directly impact the excitability of DRG neurons, through PAR-4 activation	Sessenwein et al. (2017)
Bacterial component/metabolites	Molecular recognition/mechanisms	References
Expression of specific receptors potentially implicated in bacteria—neurons communication		
SCFAs	GPR41, one of the receptor for SCFAs, is expressed in various parts of the peripheral nervous system including nodose neurons, DRG neurons and sympathetic ganglia neurons	Nøhr et al. (2015)
Flagellin	TLR5 is expressed in mouse DRG neurons	Xu et al. (2015)

Table 1 (continued)

Bacterial component/metabolites	Molecular recognition/mechanisms	References
Peptidoglycan, lipoteichoic acid, lipopolysaccharides	TLR2, TLR3 and TLR4 induce the activation of microglia and astrocytes and the production of the proinflammatory cytokines in the spinal cord, leading to the development of inflammatory pain. TLRs are new players in the processing of pain by increasing the excitability of primary sensory neurons	Liu et al. (2012)
Others	Both human and mouse DRGs express TLR3/7/9. Murine stimulated with TLR3/7/9 ligands increase mRNA expression and protein production of many inflammatory cytokines and chemokines, previously identified as mediators of pain hypersensitivity	Qi et al. (2011)

immunoactive fibers in colonic biopsies from patients with IBD or IBS (Akbar et al. 2008). Another pathway of LPS recognition exists. In fact, LPS can also activate TRPA1 channels (Meseguer et al. 2014). TRPA1 channels are key participants in the biological response to LPS, because they do not need TLR4 to be activated and to induce neurogenic inflammation. TRPA1 is expressed in a smaller proportion (20–30%) of sensory neurons that often express neuropeptides (substance P and CGRP). Besides being expressed in extrinsic afferents, TRPA1 is expressed by enteric neurons and non-neuronal enterochromaffin cells (EC) in the gut (Lai et al. 2017). LPS modulates TRPA1 activity by inducing mechanical perturbations in plasma membrane of neuronal cells leading to release of neuropeptides, local inflammation and sustained mechanical hyperalgesia (Meseguer et al. 2014). Finally, authors hypothesized that TRPA1 channels and patterns receptors like TLR4 act as synergic sensory mechanisms, altering the host about the presence of pathogens, allergens and environmental irritants. Besides being recognized by TLR4 and TRPA1, other receptors can be activated by LPS such as transient receptor potential melastatin member 3 (TRPM3) and 8 (TRPM8) at 25 °C (but not at 35 °C), but not by TRPV2 which is insensitive to LPS. Finally, LPS can activate several receptors. Among them, TRPA1 remains the most sensitive sensory TRP channel, whereas TRPV1 requires a higher dose of LPS (Boonen et al. 2018). TLR3 and TLR7 are expressed in neurons and glial cells of the myenteric and submucous plexuses of murine small and large bowel and in plexuses of the human ileum (Barajon et al. 2009). The expression of TLR3 and TLR7 suggests that a surveillance system exists regardless of immune response. As seen in the precedent part of the review, flagellin is recognized by TLR5 and NLRC4 (Ley and Gewirtz 2016) and because TLR5 is expressed in DRG neurons, we can hypothesize that flagellated bacteria can activate sensory neurons and pain perception; this is a new way of exploring new therapeutic targets (Xu et al. 2015). *N*-formyl peptides are motifs found in bacteria and recognized by FPRs. In addition to activate immune response, they can also induce inflammatory pain by interacting with nociceptors. It is the case of *Staphylococcus aureus* whose *N*-formyl peptide is recognized by FPR1 leading to pain perception and release of immunosuppressive neuropeptides (Chiu et al. 2013). Indeed, it has been recently demonstrated that FPR1 is expressed on the enteric neurons and the critical role of FPR1 in the regulation of enteric signaling and gut motility (Chandrasekharan et al. 2019).

The question is why do we have two systems of defense to fight against pathogen invasion? Expression of TLR3, TLR4 and TLR7 by the enteric neural network suggests that virus and bacteria could directly recognize and activate intestinal neural responses without the intervention of immune system. This direct interaction between sensory neurons and bacterial or viral agents could constitute the first piece of information about intestinal microorganisms, transmitted to the CNS (Barajon et al. 2009). If we focus at the intestinal level, it is interesting to learn that IPANs express innate immune receptors, including TLR2, TLR3, TLR4 and TLR7 that enable detection of pathogen-associated molecular patterns. It was found that the capsular polysaccharide A of *Bacteroides fragilis*, a symbiotic strain of the gut microbiota can induce activation of sensory neurons. The fact that polysaccharide A (PSA) alone can induce this response and that whole bacteria is not necessary to activate sensory neuron is an open gate to a better understanding of the mechanisms of interaction involved between symbiotic bacteria and the host and their implication in chronic pain in case of dysbiosis (Mao et al. 2013). Amuc_1100, a protein isolated from the outer membrane of the strain *Akkermansia muciniphila*, one of the most abundant members of the human gut microbiota, can activate cells expressing TLR2 (Plovier et al. 2017). The expression of TLR in neuron cells has been demonstrated in many studies and has to draw our attention because of their potential implication for both acute nociceptive response and the maintenance of chronic pain states. In addition, multiple factors could influence the magnitude of effects leading to pain perception, including: (1) ability of bacteria to directly access the bowel sensory neurons, (2) the expression

level of TLRs which can be increased during inflammation (Fukata and Abreu 2007, 2009) such as TLR2, TLR4 and TLR5 which are upregulated in IBD (Brint et al. 2011; Cario and Podolsky 2000), (3) and the nature of the bacterial cell products that translocate into the tissues. The possible direct interaction between pathogen and neuron is not fully understood yet but recent evidences of a contact and an activation of nociceptors by *Staphylococcus aureus* allow us to extend our investigations on this field. Indeed, beneficial effects supported by several members of gut microbiota have to be described at the mechanistic level. It is clear that direct activation constitute a novel pathway of pain induction and by extension hypersensitivity often encountered in case of chronic inflammation and IBD. A better understanding of the mechanisms involved becomes a necessity to identify new therapeutic strategies in the prevention of development and in reduction of chronic pain.

Interaction with metabolites

Bacteria and particularly those belonging to the gut microbiota are able to produce large numbers of metabolites that can influence the immune response and pain perception via the activation or inhibition of nociceptors (Fig. 2). In fact, many of these metabolites constitute ligands of nociceptors. Among these, bacteria can product SCFAs (Morrison and Preston 2016), toxins (Marion et al. 2014), neurotransmitters (Strandwitz 2018), capsular polysaccharides (Blandford et al. 2019) or anti-inflammatory proteins (Quévrain et al. 2016) depending on the strain. The beneficial effects of SCFAs are well documented. It has been found that FFAR3, receptor activated by short-chain fatty acids is not only expressed in enteroendocrine cells but also in postganglionic sympathetic and sensory neurons in both autonomic and somatic peripheral nervous system that potentially make a possible interaction between microbial metabolites and nervous system (Nøhr et al. 2015). These metabolites are the result of a fermentation of undigested complex carbohydrates by gut microbiota, and takes place more specifically in the colon depending on multiple factors such as composition of gut microbiota, the fiber content of the host diet and so on. SCFAs constitute an energy source for colonocytes and maintain colonic epithelium homeostasis. Specific members of gut microbiota participate in the phenomenon of cross-feeding. In fact, lactate can be metabolized to acetate, propionate or butyrate by cross-feeding organisms (Morrison et al. 2006; Ríos-Covián et al. 2016). For example, *Faecalibacterium prausnitzii* and *Roseburia* sp. metabolize acetate produced by other microorganisms (Duncan et al. 2004) and a study demonstrated that *F. prausnitzii* has the capacity to use acetate previously released by the strain *Bacteroides thetaiotaomicron* (Wrzosek et al. 2013). While metabolic pathway of acetate is widely distributed within gut microbiota, production of propionate or butyrate is insured by several specific species. For example, *Akkermansia muciniphila* (Derrien et al. 2004) is involved in production of propionate, whereas *Ruminococcus bromii* and *Faecalibacterium prausnitzii* have been identified as the major producers of butyrate (Louis et al. 2010). There is a real symbiosis between bacterial strains through a metabolic dialogue. The gut microbiota plays an important role in mucosal, neuronal and systemic 5-HT homeostasis via SCFAs production, because they can potentially affect serotonergic regulation by promoting colonic serotonin production by enterochromaffin cells (Reigstad et al. 2015). SCFAs have other several biological properties at the colon level. First, they have an impact on the luminal pH leading to an acidification that can limit the growth of pathogenic microorganisms (Macfarlane and Macfarlane, 2012). Second, they have an anti-inflammatory effect by inactivating nuclear factor-κB (NF-κB) and by decreasing the release of proinflammatory cytokines (Rooks and Garrett 2016) and inhibiting histone deacetylation (HDAc) (Donohoe et al. 2014). SCFAs also play an important role by maintaining epithelial integrity (via the regulation of tight junction and the expression of Zonula occludens-1 and Claudin-1) (Wang et al. 2012). Lastly, they increase mucin production (Jung et al. 2015).

Several mechanisms have been proposed to explain the beneficial effect of butyrate in visceral pain perception. First, butyrate could modulate serotonin release (which can increase the compliance of the hollow viscera leading to decrease in perception) or activate of TRPV1 receptors in the colonic mucosa by butyrate which may indirectly lead to serotonin release or induce a deactivation of TRPV1 channels by repetitive stimulations. Despite all results obtained in the colon of rats, differences observed in human were not excluded due to differences in microbial composition and in metabolism of butyrate (Kannampalli et al. 2011). Thus, we can hypothesize that these metabolites can directly act on nociceptors and have also a role in pain perception, because one of their receptor G-coupled receptor 41 (GPR41) is expressed on enteric nerves, in ganglia cells of both submucosal and myenteric ganglia (Inoue et al. 2012; Kimura et al. 2011; Nøhr et al. 2013).

Another group of metabolites that can modulate pain perception are represented by neurotransmitters. Bacteria have been found to be able to produce a wide range of neurotransmitters including catecholamines (dopamine and norepinephrine), serotonin (5-HT), noradrenaline, GABA, acetylcholine and histamine (Strandwitz 2018). The production of these compounds has been well described specifically among genus like *Lactobacillus* and *Bifidobacterium*. It is the case of GABA, which represents the major inhibitory neurotransmitter of the central nervous system. Production of GABA by bacteria constitutes a strategy leading to a decrease in intracellular pH (Feehily and Karatzas 2013).

Another compound can modulate pain perception, 5-HT, a signaling molecule, produced by both enterochromaffin cells and several bacteria of gut microbiota, is able to signal sensory neurons and is implicated in visceral pain. In fact, serotonin can activate transient receptor potential vanilloid member 4 (TRPV4) by three different pathways: (1) by the phosphorylation of TRPV4 by phospholipase C and protein kinase C which increase TRPV4 agonist-induced calcium signaling, (2) by the translocation of TRPV4 from the nuclear zone to the plasmic membrane, (3) by the potentiation of TRPV4 by a phospholipase A2 (Cenac et al. 2010).

In addition, the gut microbiota may be an important regulator of circulating tryptophan availability, molecular precursor of serotonin. There is a balance between tryptophan utilization and metabolism that is determined at the gastrointestinal level and tryptophan availability for the host. Amongst its many functions, serotonin is a key regulator of pain modulation through the activation of extrinsic afferent spinal and vagal nerves. Correlation between 5-HT release in gastrointestinal tract and pain in IBS patients has been shown (O'Mahony et al. 2015). The use of probiotic bacteria that can deliver neurochemicals has been also suggested as a novel treatment for neuropsychiatric diseases (Lyte 2011).

Generally speaking, there is a link between altered neurotransmission and neurological disorders and pain (Strandwitz 2018). Finally, it is easy to imagine that the interaction between gut microbiota and enteric nociceptors can occur via metabolites that they are able to produce. However, those interactions need to be better investigated at the mechanistic level to fully understand how the microbiota could modulate pain perception and to identify novel therapeutic strategies. Sessenwein et al. have demonstrated that commensal gut bacteria can directly impact the excitability of DRG neurons, through PAR-4 activation and this represents an important first step which leads to a better comprehension of the ability of gut microbiota to modulate neuronal activation (Sessenwein et al. 2017).

Conclusion and perspectives

Painful conditions are strongly disabling because of the significant alteration of the patients' "well-being". Pain is one of the major symptoms from patients with intestinal barrier dysfunction as well as mucosal inflammation or altered motility. These patients often suffer from associated behavioral disorders such as anxiety or depression (Vivinus-Nébot et al. 2014). The role of the gut microbiota in the pathophysiology of such intestinal disorders is suggested by the presence of risk factors such as host genetics, stress, diet, antibiotic therapy, infections or occurrence of traumatic events during infancy, which can modulate the composition of the microbiota. In addition, it is now clear that certain bacterial pathogens are capable of producing effectors that can directly activate sensory neurons that subsequently modulate the host's response to infection (including inflammatory response or defensive behaviors), demonstrating an unsuspected role for the nervous system in host–pathogen interactions. This review stressed the importance and possible etiological role of the microbiota in chronic pain and discomfort. In regard to this review, innovative therapeutic strategies targeting the microbiota could be considered, for pain management (Chassard et al. 2012; De Palma et al. 2017).

At present, many studies are being carried out to understand the interactions between microorganisms and eukaryotic cells. However, there is little interest in the direct dialogue between these microbes and neuronal cells, which are nevertheless primordial cells in host pain control. Thus, more work needs to be done on these interactions to better understand the impact and possible mechanisms linking microbiota and pain perception. For that purpose, the use of calcium imaging tools could lead to the characterization of new microbial ligands that may be responsible for an abnormal modulation of neuronal activity.

Different types of microbiome-based therapeutic approaches could be investigated in the coming few years (Valencia et al. 2017): (1) whole microbiome transplants is an intervention that introduces microbiota from a healthy donor into a patient to correct severe intestinal dysbiosis such as shown with *Clostridium difficile* infection. Beneficial effects of microbiome transplant could be investigated for other painful diseases such as chronic intestinal diseases but also extra-intestinal pathologies. (2) "Bugs as drugs" or probiotics can be used to act on the microbiome by introducing known beneficial microbes into a patient. One interesting approach is to engineer microbes that produce beneficial factors after introduction into the gut. (3) Prebiotics and contrabiotics can favor or block particular microbiota populations through paracrine signaling and thus modify the microbiome composition and its structure. (4) Next-generation antibiotics could be used to target drug-resistant microbial strains and provide alternatives that avoid major side effects on the microbiome. (5) Host–microbiome interaction pathways are being explored based on the analysis of metabolites produced by the microbiome, the goal being to restore the activity of the microbiome by introducing signaling molecules, typically produced through gut fermentation, that can act on known pathways—'microbiome mimics'.

Given the growing interest of gut microbiota modulation as a therapeutic target, Gilbert et al. proposed a pipeline for therapeutic strategies for neurodevelopmental disorders based on microbiome and metabolite profiling (Gilbert et al. 2013). This pipeline recommends to use disease mouse model as a first step to understand the importance of specific gut microbes and their metabolites in pathogenesis. Then,

results would be tested and validated in preclinical models by altering the microbial community and/or metabolite profile to restore the healthy state. Finally, new analogous treatments could be formulated and applied in human clinical trials.

Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

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