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Effect of commensals and probiotics on visceral sensitivity and pain in irritable bowel syndrome

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The last ten years' wide progress in the gut microbiota phylogenetic and functional characterization has been made evidencing dysbiosis in several gastrointestinal diseases including inflammatory bowel diseases and irritable bowel syndrome (IBS). IBS is a functional gut disease with high prevalence and negative impact on patient's quality of life characterized mainly by visceral pain and/or discomfort, representing a good paradigm of chronic gut hypersensitivity. The IBS features are strongly regulated by bidirectional gut-brain interactions and there is increasing evidence for the involvement of gut bacteria and/or their metabolites in these features, including visceral pain. Further, gut microbiota modulation by antibiotics or probiotics has been promising in IBS. Mechanistic data provided mainly by animal studies highlight that commensals or probiotics may exert a direct action through bacterial metabolites on sensitive nerve endings in the gut mucosa, or indirect pathways targeting the intestinal epithelial barrier, the mucosal and/or systemic immune activation, and subsequent neuronal sensitization and/or activation.

Introduction

The human intestine harbors a vast and complex microbial ecosystem called microbiota linked to the host by a symbiotic relationship leading to gut homeostasis. Thus, for the bacterial prokaryote the alimentary tract offers a supply of nutrients and inversely the host benefits from bacterial metabolism products and complex interactions leading to immune and non-immune host defense. Bacteria are the main microorganisms (there are also representatives from archaea and eukarya as well as viruses[1]) composing this ecosystem, but their species and number remained largely underestimated, before the rapid evolution of molecular approaches occurring in the last ten years. Currently, the number of bacterial species identified in human fecal samples exceeds 1000.[2] The normal gut microbiota of adult humans is stable over time and highly resilient to transient aggression.[3] However, a breakdown in the mutualistic microbiota-host relationship, called dysbiosis, has been observed in several gastrointestinal pathologies, such as inflammatory bowel diseases (IBD)[4,5] and irritable bowel syndrome (IBS) reflected by changes in the stability, diversity, composition, and/or metabolism of gut bacteria.[6-12] On this basis, therapeutic strategies targeting the gut microbiota have emerged as for example antibiotics[13] or probiotics use.[14] Definitely, the most striking findings coming mostly from animal studies highlight that gut microbiota, or its modulation by antibiotics or probiotics can exert effects beyond the gut targeting spinal or supraspinal sites of action and strongly support the concept of the microbiota-gut-brain axis (for a review see ref. 15). Interestingly, in addition to gut dysbiosis, visceral pain, and psychiatric co-morbidity are common features in functional gastrointestinal disorders, such as IBS.[16] This encouraged investigations using IBS-like animal models to explore the microbiota-gut brain interactions and contribute in the understanding of IBS physiopathology. In this text we will focus on the effects and mechanisms of action of gut microbiota and probiotics on visceral pain based on animal studies and we will discuss the relevance of gut microbiota modulation probiotics in IBS.

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Visceral Sensitivity in IBS: The Top Down and Bottom Up Hypotheses

IBS is a common and highly prevalent disorder which affect, according to the diagnosis Rome criteria applied, 5–20% of the global population.[17,18] Despite high prevalence the precise etiology and pathophysiology of IBS remains poorly understood and is often referred as multifactorial. IBS is a good paradigm of chronic gut hypersensitivity and visceral pain, defined as an unpleasant sensation which in contrast to somatic pain remains diffuse and difficult to localize.[19] Accordingly, Ritchie et al. in 1972 reported that chronic abdominal pain in IBS patients is associated with lower visceral painful sensations in response to repeated inflations of a rectal balloon.[20] However, visceral sensitivity to rectal distension is not a universal feature of IBS patients. Accordingly, the literature reports only 21 to 94% of IBS patients as hypersensitive to rectal distension, evidencing the presence of normosensitive individuals among this population and suggesting distinct pathophysiology pathways involved.[2] For instance, patients with visceral hypersensitivity to colorectal distension reported increased pain responses to rectal application of

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capsaicin, a TRPV1 agonist when compared with normosensitive IBS patients and healthy controls.[21] Other predominant IBS features are changes in bowel habits and bloating[22] originating from intestinal motility changes and gut abnormal fermentations respectively.[23] Gut microbiota composition, stability, and functional changes have also been reported in IBS.[6-12] The phylogenetic microbial characterization is conducted mainly from fecal samples. Despite the lack of identification of a specific microbial group characteristic for IBS dysbiosis the alterations generally reported concern the Bifidobacterium and Clostridium coccoides-E. rectal subgroup.

The overall of these IBS features occur without identifiable organic cause and are strongly influenced by stress and anxiety suggesting the involvement of brain-gut interactions in this disease.[24] The origin of visceral hypersensitivity in IBS can be central and/or peripheral (for review see ref. 25). The first works on the mechanisms involving the brain-gut axis were based on the communication between the gut intrinsic innervation (enteric nervous system; ENS), connected on the extrinsic innervation (the autonomic nervous system), which interacts with the hypothalamic-pituitary axis and affects visceral sensory motor functions.[26] The input from splanchnic visceral afferences is received in the spinal dorsal horn and from this site second-order neurons transmit the visceral sensory information to supraspinal sites, the final integration of the painful perception occurring in the cortex.[27] Vagal afferences activation plays a modulatory role on the spinal visceral pain pathway.[28] In IBS, increased neuron excitability resulting to visceral hypersensitivity has been reported at several levels of the brain-gut axis, i.e., ENS, spinal cord and supraspinal sites.[29] In the supraspinal sites interactions with emotional or stressful influences can modulate the visceral sensitivity resulting to increased pain perception.[30]

Besides central influences on visceral sensory function in IBS, peripheral factors such as luminal agents (bacteria, or microbial antigens) may also establish a cross-talk with the brain-gut axis and contribute to IBS visceral hypersensitivity. A strong support to this hypothesis was the evidence indicating that IBS may be the adverse outcome of an acute episode of gastroenteritis characterized as post-infectious IBS (PI-IBS) and was proposed 50 years ago by Chaudary and Truelove.[31] Interestingly, increased intestinal paracellular permeability has been reported in these patients both in a study investigating persistent IBS symptoms after *Campylobacter jejuni* infection or after a large waterborne outbreak of acute gastroenteritis in Canada.[32,33] Further, a posteriori investigations of the Canada outbreak highlighted genes encoding for proteins involved in epithelial cell barrier function and the innate immune response to enteric bacteria, which may be considered as potential genetic determinants of PI-IBS.[34]

More recently, prospective studies have shown that 3% to 36% of enteric infections lead to persistent new IBS symptoms, the precise incidence depends on the infecting organism.[35] Interestingly, the microbiota profile analysis in PI-IBS patients revealed that several members of Bacteroidetes phylum were increased 12-fold in patients, while healthy controls had 35-fold more uncultured Clostridia. Further, the particular PI-IBS microbiota profile was positively correlated with host gene expression related to epithelial cell junction integrity and inflammatory response.[36] Systemic immune activation against bacterial luminal antigens has also been described in IBS and particularly in PI-IBS, since antibodies against flagellin (the primary structural component of bacterial flagella) were observed more frequently in IBS vs. healthy controls and among IBS population these antibodies were more frequent in the PI-IBS subset.[37] Another argument supporting the contribution of luminal bacteria in the visceral hypersensitivity is related to functional dysbiosis and altered intestinal fermentation described in IBS. Chassard et al.[12] report increased sulfate-reducing bacteria population in fecal microbiota of constipated predominant IBS patients (IBS-C), producing more sulfides,[12] known to enhance visceral nociception[38] and H_2 able to generate gas-related symptoms such as bloating and flatus.[39] Abnormal intestinal fermentation in IBS has also been described in the small intestinal bacterial overgrowth (SIBO) hypothesis, where a 4-fold greater rate of maximal gas excretion and greater total hydrogen production in the presence of a fermentable substrate was described.[40] Interestingly, antibiotic treatment leading to SIBO eradication improved also IBS symptomatology.[41] Moreover, antimicrobials targeting IBS management, have also been used in clinical trials and experimental studies. These are mainly locally acting antibiotics for obvious reasons of systemic antibiotics related adverse effects. The efficacy of neomycin (a poorly absorbed aminoglycoside antibiotic) was tested in IBS-C population.[42] Constipation was improved by 32.6 ± 9.9% with neomycin vs. 18.7 ± 7.2% for placebo. Further the methane producers IBS-C patients treated by neomycin exhibited higher constipation improvement vs. placebo suggesting that this improvement depends on the elimination of methane on breath test.[42] Another study from the same group has shown that neomycin normalized lactulose breath test in IBS leading to a marked decrease of IBS symptoms.[43] However for safety reasons[44,45] the use of neomycin for IBS symptoms improvement seems inadequate. Strong clinical evidence in IBS emerged concerning the efficacy of rifaximin, a synthetic derivative of rifamycin acting locally in the gastrointestinal tract and used commonly for the traveler's diarrhea. In a phase III double-blind placebo-controlled trial, a two week treatment by rifaximin induced an improvement of the IBS symptoms such as bloating, abdominal pain and stool consistency and had a response to treatment during the first 4 weeks after completion of the treatment vs. the placebo group.[46] In a phase IV trial evaluating the efficacy of rifaximin in IBS patients, the authors confirmed previous data and reported that rifaximin improved IBS symptoms for 3 months following 2 weeks treatment in lactulose hydrogen breath test-positive IBS patients.[47] These clinical data clearly support the involvement of microbiota in the IBS pathogenesis and visceral pain.

Regarding the rate of the main bacterial metabolites issue from intrestinal bacteria fermentation, namely short chain fatty acids (SCFA), production in IBS as well as their influence on the associated visceral sensitivity, the literature data remain contradictory. Increased SCFA production in IBS has been described with elevated severity of visceral pain in patients

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with the highest SCFA levels[48] whereas other studies reported lower concentrations of SCFA in IBS.[49] Such discrepancies can be attributed to uncontrolled diet differences among patients. Further, increased or decreased visceral nociceptive perception has been described after intracolonic instillation of butyrate.[50,51] However whether gut dysbiosis in IBS is a cause or a consequence of the disease remains unclear.

Gut Microbiota and Visceral Sensitivity: Mechanistic Aspects

The incidence of the luminal milieu (bacteria and their by-products) to the IBS associated visceral pain highlights the possibility of a cross talk between gut microorganisms and/or their metabolites, intestinal barrier, mucosal immunity and neural pathways. It has been recently shown that visceral hypersensitivity characterizing IBS-C patients can be transferred to rats by the fecal microbiota.[52] Accordingly, germ free rats inoculated with IBS-C fecal suspension exhibited increased visceral sensitivity in response to colorectal distension compared with germ free rats inoculated with healthy controls fecal suspension in absence of any mucosal abnormality and change in gut permeability.[52] In contrast, germ free rats inoculated with IBS-C microbiota presented abnormal gut fermentation mostly characterized by increased H_2 excretion and sulfides production vs. controls.[52] Authors suggest that H_2 and hydrogen sulfide may be bacterial metabolites responsible for visceral hypersensitivity since H_2 increased production has been described in IBS[39] and colorectal infusion of hydrogen sulfide directly triggers visceral nociceptive behavior in mice through sensitization and/or activation of T-type channels probably in the primary afferents.[38] Besides direct action of bacterial metabolites on sensitive terminals, pathways involving epithelial barrier and neuro-immune interactions may also occur. Interestingly, the presence of a low grade inflammation in the gastrointestinal tract of several IBS subtypes has been described.[53] This inflammatory tone involving neuro-immune interactions in the gut mucosa may generate mediators able to sensitize nerve afferents resulting to viscera hypersensitivity. Indeed, in addition to mechanosensitive receptors and plymodal endings the gut also contains a class of mechanically insensitive receptors called "silent" receptors which may respond to mechanical stimulation after organ insult such as inflammation and amplify visceral sensitivity.[54]

In rodents, antibiotic treatment altering gut flora, was associated with increased colonic inflammatory tone and substance P (a sensory neurotransmitter) immunoreactivity, resulting to visceral hypersensitivity.[55] The involvement of neuro-immune interactions is further supported by findings showing that IBS patients have significantly increased number of immune cells in the gut mucosa, such as T cells[32] and mast cells[56,57] and increased fecal levels of human β-defensin 2 (HBD-2)[58] indicating activation of the innate immune system compared with controls. Interestingly, T cell activation induces changes in the enteric neuromuscular function[59] and the colonic mast cells infiltrate in IBS is closer to enteric nerve endings vs. controls as well as positively correlated with severity and frequency of abdominal pain or discomfort.[60] Moreover, mediators released from colonic IBS biopsies such as histamine serotonin and mast cell proteases can activate human submucosal enteric neurons possibly contributing by this way to visceral hypersensitivity.[61] Besides mast cells, colonic bacteria are also able to release proteases.[62] For instance, *Lactobacilli* exhibiting high ability to cleave proteases (anti-protease activity) are decreased in IBS diarrhea-predominant patients (IBS-D).[7,9] Interestingly, an increase in fecal serine-protease activity mostly from microbial origin has been observed in IBS-D patients compared with controls and IBS-C patients.[63] Further, the intracolonic application of IBS-D fecal supernatants in mice, increased colonic paracellular permeability and induced visceral hypersensitivity through a protease activated-receptor type 2 (PAR2) pathway.[64] More recently an increase in luminal cysteine-protease activity was described in a subset of IBS-C patients positively correlated with disease severity and abdominal pain scoring.[65] Further, repeated colonic mucosal application in mice of fecal supernatant from this subset of IBS-C patients induced gut hyperpermeability linked to the enzymatic degradation of occludin, and was associated with enhanced visceral sensitivity.[65] As pointed by these studies the intestinal epithelial barrier regulating the trans and paracellular passage in the gut represents another key factor in the communication between the luminal milieu, mucosal immunity and nerve endings. Interestingly, increased gut permeability has been described in IBS patients whatever the sub type considered[66] and a positive correlation between increased gut paracellular permeability and visceral pain and discomfort has been shown.[67] In a recent study the increased number of mast cells determined in the jejunum of IBS-D patients was found associated with intestinal epithelial apical junction complex alterations as reflected by reduced occludin phosphorylation and redistribution in the cytoplasm and enhanced MLCK phosphorylation.[68] Further, these changes at the proteic level were associated with ultrastructural abnormalities at the apical junction complex, i.e., perijunctional cytoskeleton condensation and enlarged apical intercellular distance clearly evoking epithelial barrier impairment.[68] In another study of the same group, investigating IBS-D biopsies, reduced zonula occludens 1 (ZO-1) expression in the jejunum and redistribution in the cytoplasm have also been reported.[69] More interestingly, these epithelial barrier defects were correlated with increased number of mast cells and clinical symptoms.[69] Taken together these data underline the major role of epithelial barrier impairment in the IBS pathogenesis. Moreover, animal studies highlight a cause effect relationship between gut hyperpermeability and visceral hypersensitivity induced by stress.[70] Indeed, in rats blockade of the intestinal epithelial cell cytoskeleton contraction (by a MLCK inhibitor, ML-7), and subsequent tight junctions opening, prevented visceral hypersensitivity induced by an acute stress.[70]

Probiotics and Visceral Sensitivity

Probiotics are defined as live microorganisms which when ingested in adequate amounts confer a health benefit on

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the host.[71] In a recent systematic review aiming at establish a reference guide on the role of specified probiotics in the management of lower gastrointestinal disorders, including IBS, by means of systematic review-based consensus, authors reported evidence of an overall benefit of probiotics use in IBS.[72] Among statements worded to reflect the grade of available evidence (high, moderate, or low), "specific probiotics help to reduce abdominal pain, bloating, and/or distension in some patients with IBS" was recorded as high.[72] However, clinical trials testing probiotics efficacy in IBS remain generally difficult to compare due to differences in the study design (size of the study, duration of the treatment), probiotic dose and strain used. Further, some of them are conducted using probiotic mixtures rather than single strains, and even combinations including prebiotics rendering difficult to decipher the active moieties and their mechanism of action. Regarding safety, an important issue in the probiotics use, Lactobacilli, Bifidobacteria, and other commensal microorganisms are generally regarded as safe. However the safety can be compromised and a risk of bacteremia can emerge when probiotics are massively administered in immunodepressed or in severe illness suffering patients.[73-75] Besides a overall beneficial but modest effect of priobiotic treatments in different meta-analyses, further investigations are clearly needed in order to establish optimal regimens (the most effective probiotic species and strains, individual or mixture administration [synergistic effect]) as well as to identify subgroups of patients most likely to benefit from these treatments.

From the mechanistic point of view, arguments in favor of the probiotics use in IBS come mostly from animal studies and are based mainly in their ability (1) to modulate visceral sensitivity and (2) to enhance intestinal barrier function and immunity. In this paragraph will be discussed literature data concerning these abilities.

Alterations in the gut microbiota and inflammatory tone induced by non absorbable antibiotics treatment enhanced visceral sensitivity and substance P expression in the colonic mucosa.[55] These effects were prevented by *L paracasei* administration.[55] In another study, treatment with live, killed, or even the conditioned medium of *L reuteri* prevented the pain response to colorectal distension, as reflected by inhibition of the constitutive cardio-autonomic response to colorectal distension and decrease in the dorsal root ganglion single unit activity to distension.[76] A decrease of normal visceral perception and chronic colonic hypersensitivity, elicited by butyrate enemas, was also observed after an oral treatment by *L acidophilus* NCFM.[77] This effect was associated with an increased expression of μ-opioid (MOR1) and cannabinoid receptors (CB2) in intestinal epithelial cells.[77]

Acute and chronic stress models are widely used as IBS-like models, since stress induces gut hyperpermeability and visceral hypersensitivity in response to colorectal distension.[78,79] The ability of probiotic strains to enhance intestinal epithelial barrier function was reported by Zareie et al.,[80] showing that a commercially available probiotic combination (*L helveticus* R0052 [5%] and *L rhamnosus* R0011 [95%] treatment) prevented the ileal epithelial barrier impairment and bacterial translocation to the mesenteric lymph nodes induced by a chronic stress (water avoidance stress).[80] Similarly, treatment by the same combination, prevented colonic epithelial barrier disruption in adult rats submitted in a maternal deprivation stress during the neonatal period.[81]

The prevention of stress-induced gut hyperpermeability has been described as responsible for stress-induced visceral hypersensitivity in rodents.[70] Accordingly, treatment by *L. farciminis* prevented stress-induced visceral hypersensitivity and colonic paracellular hyperpermeability, through a decrease of the myosin light chain (MLC) phosphorylation, responsible for epithelial cells cytoskeleton contraction and subsequent tight junction opening.[82] Further, the analgesic effect of *L farciminis* was confirmed by data showing a decrease in the enhanced Fos protein expression at the spinal (spinal cords sections S1, S2, and L6) and supraspinal (hypothalamic paraventricula nucleus) sites induced by colorectal distension in stressed rats.[83] In another study comparing the effect of three probiotic strains (*L paracasei* NCC2461 *B lactis* NCC362 and *L johnsonii* NCC533) using two stress models in rats (acute restraint stress and neonatal maternal deprivation) it has be shown that only *L paracasei* NCC2461 associated with its conditioned medium was able to restore gut permeability and visceral sensitivity alterations induced by the stress, underlying the strain specificity and the synergy between live bacteria and their metabolites generated in the medium, for the stress-induced IBS-like symptoms improvement.[84] Similarly, in a study comparing the efficacy of three probiotics (*L salivarius* UCC118, *B infantis* 35624, or *B breve* UCC2003) on the abdominal response to colorectal distension using visceral normosensitive rats (Spargue-Daweley) and visceral hypersensitive rats (Wistar Kyoto), only *B infantis* 35624 reduced the colorectal distension-induced pain behavior in both rat strains.[85] Interestingly, in a clinical trial, comparing an eight weeks treatment by *B infantis* 35624 and *L salivarius* UCC118 in IBS patients, only *B infantis* 35624 treated patients experienced a reduction in composite and individual scores for abdominal pain and/or discomfort, bloating/distension.[86] It is of particular interest that in this trial *B infantis* 35624 treatment normalized the low IL-10/IL-12 ratio (indicative of a Th1 profile) characterizing the IBS patients before treatment, suggesting that the antinociceptrive effect of this strain is linked to a decrease of the IBS inflammatory tone.[86] The beneficial effects of probiotic isolated strains on stress-induced gastrointestinal disturbances can be extended to treatments with fermented dietary products containing probiotics. Accordingly, it has been recently shown that treatment with a fermented milk containing *B lactis* CNCM I-2494 and yogurt strains reduced stress-induced visceral hypersensitivity by normalizing intestinal epithelial barrier via a synergistic interplay between the different probiotic strains and/or metabolites contained in this product.[87]

Conclusions

The understanding of the role of microbiota in the bidirectional cross talk between the gut and the brain is definitively a new and fascinating research field. As such, the mechanisms of action involved in the visceral pain modulation and even more generally

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in the central nervous system influences by the microbiota are not yet clearly established. Many questions at different levels need answers. For instance, (1) regarding the long lasting effects of neonatal stress in the visceral sensitivity and gut epithelial barrier integrity, a new challenge may be the determination of the gut's bacteria role in this persisting imprinting. (2) If disturbances of the gut microbiota are observed in several pathologies it is not known if they are cause or consequences of the pathology. Further, in our opinion the functional characterization approach in the IBS dysbiosis may be more informative, at least from a mechanistic point of view, than phylogenetic characterization (3) if modulation of the gut microbiota by probiotics or antimicrobial compounds leads to observable effects there is need to understand the specificity of each agent in the precise effect and to decipher the molecular basis in the dialog with the gut and beyond the gut.

Disclosure of Potential Conflicts of Interest

No potential conflict of interest was disclosed.

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