Probiotics for Specific Treatment of Pain in Irritable Bowel Syndrome: A Review

María Ortiz Lucas, Lic,[1] Aurelio Tobías,[2] Pablo Saz Peiró, MD,[3] Juan José Sebastián, MD.[4]

1 BSc and Credential in Biochemistry, Professor in the Faculty of Health Sciences at the Universidad San Jorge in Zaragoza, Spain
mariaortizlucas@gmail.com
2 Investigator at IDAEA (Instituto de Diagnóstico Ambiental y Estudios del Agua -Institute of Environmental Assessment and Water Research, CSIC. Barcelona, Spain
aurelio.tobias@gmail.com
3 Professor in the Faculty of Medicine at the Universidad de Zaragoza in Zaragoza, Spain
pablosaz@unizar.es
4 Professor in the Faculty of Medicine and Chief of Gastroenterology at the Hospital Royo Villanova in Zaragoza, Spain
jjsebastian@salud.aragon.es

Abstract
Abdominal pain is one of the least well tolerated symptoms in patients with irritable bowel syndrome (IBS). Studies conducted in recent years suggest that dysbiosis in these patients may be responsible, at least in part, for these symptoms. This literature review indicates that probiotics may be an effective therapy for the relief of pain in patients with IBS and recognizes that the effects of probiotics are specific to the strain used. In this article we review the effect that each strain or mixture of probiotics has for relieving abdominal pain according to published clinical trials and we also discuss possible mechanisms of action. New perspectives are proposed for research to elucidate the mechanisms of probiotic action for relief of abdominal pain in these patients.

Keywords
Probiotics, irritable bowel syndrome, abdominal pain, mechanism of action.

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IRRITABLE BOWEL SYNDROME AND MICROBIOTA

Irritable Bowel Syndrome (IBS) is the most prevalent functional digestive disorder. A diagnosis of IBS is established according to the consensual clinical criteria (Rome Criteria) which has changed throughout the years. The last consensus (Rome III, 2006) ratifies that patients with IBS must present: "*Recurrent pain or abdominal discomfort at least 3 times a month during the last three months associated with 2 or more of the following elements: improvement with defecation, onset of pain associated with a change in bowel movement frequency, onset of pain associated with a change in appearance of the feces*" (1). In recent years, increasing amounts of evidence have suggested the presence of intestinal dysbiosis in these patients, even though there is no uniform alteration in the composition of the microbiota, the group of patients with IBS or the various subtypes of IBS. There are even some authors that suggest categorizing patients into subtypes according to microbiotic profiles (2-7).

THE ACTION MECHANISM OF PROBIOTICS

Probiotics are defined as live microorganisms which provide a health benefit to the host when administered in adequate quantities (8). They have different effects in the host. Modulation of intestinal microbiota by probiotics is attributed to their capacity of transiently colonizing the gastrointestinal tract and releasing antimicrobial elements. Probiotics compete against other pathogens, preventing their replication and weakening their virulence. They also affect the functioning of the intestinal barrier by adhering to intestinal cells and maintaining the integrity and resistance of the epithelial barrier which prevents the enteric pathogens

from adhering to the intestinal cells thus preventing their effects. The anti-inflammatory effects of the probiotics have been attributed to the recruitment of immune cells and the activation of the immune response through the alteration of cytokine and chemokine release. Finally, probiotics might play a role in decreasing visceral hypersensitivity. Besides these local effects, probiotics also have the systemic effect of increasing immune protection (9-16).

In the particular case of IBS, probiotics might modify the intestinal microbiota by increasing the amount of beneficial bacteria in the gastrointestinal tract and decreasing bacterial overgrowth in the intestine. This improves functioning of the intestinal barrier by increasing intestinal permeability, inverting the imbalance between pro- and anti-inflammatory cytokines, delaying intestinal transit and modifying visceral hypersensitivity (17-21).

Although the effects of probiotic intake on microbiota have been studied in IBS patients, the studies reach different conclusions. Some authors could not demonstrate any change in intestinal microbiota after administration of probiotics (22-24). Others have found that the microbiota stabilized (25-27). The latter authors considered that stabilization of the microbiota is a positive effect since unstable microbiota have been found more frequently in IBS patients than in healthy patients (28, 29). In contrast, a recently published study has found that a change in microbiota occurred in patients treated with probiotics (30).

The scientific evidence indicates that the action mechanisms of probiotics are specific to the individual species and even to the strain of probiotic. Also, there are multiple effects on the host (9, 11, 21, 31). Abdominal pain, one of the least tolerated symptoms for IBS patients, negatively affects their quality of life (32). The literature suggests that probiotics could be an effective therapy for treating pain in some patients with IBS (33-35), however, what specific species or strains of probiotic are responsible for pain relief in IBS patients?

ANTINOCICEPTIVE EFFECT OF PROBIOTICS

Table 1 summarizes results from random clinical trials on abdominal pain relief resulting from administration of probiotics to adult patients with IBS. Only two of the studies include information on the probiotic strain or the mix of probiotics used in the studies (22, 27, 30, 36-62).

SPECIES OF PROBIOTICS

The effect of the *Lactobacillus plantarum straing* DSM 9843 (299v) on abdominal pain relief was measured in two studies (39,62). Ducrotté et al. found that the probiotic diminished pain, while Nobaek et al. found improvements at the beginning of treatment in patients given probiotics, but also in patients given placebos. Combinations of probiotics that contained *L. plantarum* did not produce any greater improvements than did the administration of placebos (22, 25, 58, 61). A study of the administration of this species of probiotic to healthy animals found both decreased pain and an anti-inflammatory effect. (63) This antinociceptive effect was not found when a painful stimulus was applied (64). Upon evaluating this species of probiotic (strain NCIMB8826) and a mutant of the strain which is deficient in D-alanine, it was found that the regulating effect of probiotics in visceral pain perception in the colon could be related to the degree of D-alanylation of membrane-associated lipoteichoic acid. The researchers proposed that anti-inflammatory cytokines could also be involved in decreasing the perception of visceral pain (63, 65). However, the antinociceptive action mechanism seems to be specific to the combination of probiotic strain and target organ (64).

Two studies have found a positive effect of the *Bifidobacterium infantis* 35624 strain in the treatment of abdominal pain (56, 57). Nevertheless, Charbonneau et al. were unable to confirm this effect (36). Whorwell et al. found that this effect was significant in patients whose predominant symptom was constipation (56). Administration of the VSL#3 mix of probiotics which contains this species provided no additional abdominal pain relief (22, 58, 61). A visceral antinociceptive effect of strain *B. infantis* 35624 has been found in healthy rats, rats with an anxiety profile and rats with post-inflammatory colon hypersensitivity (66, 67). O'Mahony et al. found positive relief of abdominal pain accompanied by a modulation in immune response through reestablishment of the IL-10/IL-12 ratio in the probiotic group (57). However, the study provides no data on correlations between these two factors. Duncker et al. suggest that there might be a relation between the levels of cytokines and the nociceptive capacity of the nervous system, which could explain the results of O´Mahonny et al (63).

A positive effect of the *Bifidobacterium bifidum* MIMBb75 strain has been shown in one abdominal pain treatment study (43). Three other studies have employed other strains of *B. bifidum* as part of probiotic mixes (30, 49, 50). Patients who were treated with a probiotic mix containing the *B. bifidum* BGN4 also showed improvements in abdominal pain (49). Those treated with a mix containing *B. bifidum* (KCTC 12 199BP) strain showed a greater tendency to improve (p=0.07) than did the control group (30). In this case, the group treated with probiotics showed a significant improvement at the beginning of the treatment which was not observed in the control group. A group treated with a probiotic mix that included the *B. bifidum* CUL-20 (NCIMB 30153) strain had results that did not differ

Table 1. Effects of probiotics in abdominal pain treatment of IBS patients.

Probiotic strain	Study (ref.)	Nº of patients	Dosage	Treatment duration	Pain measurement scale	Results
Lactobacillus plantarum DSM 9843 (299v)	Ducrotté, 2012 (26)	204	10 billion UFC	4 weeks	AVS 0-10	Improvement in TG vs CG
	Nobaek, 2000 (49)	52	$5 \cdot 10^7$ UFC	4 weeks	AVS 0-10	No differences in TG vs CG Improvements in TG‡ and in CG‡
Bifidobacterium infantis 35624	Charbonneau, 2013 (23)	61	$1 \cdot 10^9$ UFC	8 weeks	Scale 0-5	No differences in TG vs CG
	Whorwell, 2006 (43)	293	$1 \cdot 10^8$ UFC	4 weeks	Scale 0-5	Improvements in TG2¥ vs CG
	O´Mahony, 2005 (44)	72	$1 \cdot 10^{10}$ UFC	8 weeks	AVS 0-10 y Likert	Improvements in TG vs CG*
Bifidobacterium bifidum MIMBb75	Guglielmetti, 2011 (30)	119	$1 \cdot 10^9$ UFC	4 weeks	Scale 0-6	Improvements in TG vs CG
Lactobacillus salivarius spp. *salivarius* UCC4331	O´Mahony, 2005 (44)	72	$1 \cdot 10^{10}$ UFC	8 weeks	AVS 0-10 y Likert	Improvements in TG vs CG§
Escherichia coli Nissle 1917	Kruis, 2012 (27)	103	$2{,}5\text{-}25 \cdot 10^9$ UFC	12 weeks	AVS 0-100	Improvements in TG‡ and in CG‡
Saccharomyces boulardii	Kabir, 2011 (28)	70	500 mg	30 days	Scale 0-3	No differences in TG vs CG
	Choi, 2011 (29)	67	$2 \cdot 10^{11}$ UFC 2 v/d	4 weeks	Scale 0-6	
Bacillus coagulans GBI-30 6086	Dolin, 2009 (34)	52	$2 \cdot 10^9$ UFC	8 weeks	AVS 0-100	No differences in TG vs CG
	Hun, 2009 (35)	44	$8 \cdot 10^8$ UFC	8 weeks	Scale 0-5	
Lactobacillus reuteri ATCC 55730	Niv, 2005 (47)	39	$5 \cdot 10^7$ UFC 2 v/d	6 months	AVS 0-100	No differences in TG vs CG
Lactobacillus casei rhamnosus LCR35	Dapoigny,2012 (25)	47	$2 \cdot 10^8$ UFC 750 mg	4 weeks	AVS 0-100	No differences in TG vs CG

Probiotic mixes	Study (ref.)	Nº of patients	Dosage	Treatment duration	Pain measurement scale	Results
B. lactis DN-173 010, *S. thermophilus* and *L. bulgaricus*	Roberts, 2013 (24)	109	¶ 2 v/d	6 weeks	Scale 0-6	Improvements in TG‡ and CG‡
	Agrawal, 2009 (38)	34	¶ 2 v/d	27 days	Scale 1-6	Improvements in TG vs CG
	Guyonnet, 2007 (42)	267	¶ 2 v/d	6 weeks	Scale 0-6	Improvements in TG‡ and CG‡
B. bifidum BGN4, *B. lactis* AD011, *L. acidophilus* AD031, *L. casei* IBS41	Hong, 2009 (36)	68	$2 \cdot 10^6$ UFC 2 v/d	8 weeks	AVS 0-100	Improvements in TG vs CG
L. acidophilus SDC 2012 and 2013	Sinn, 2008 (41)	40	$2 \cdot 10^9$ UFC	8 weeks	Scale 0-10	Improvements in TG vs CG Improvement in TG‡
L. bulgaricus, S. thermophilus, L. paracasei ssp. *paracasei* F19, *L. acidophilus* La5 and *B. lactis* Bb12	Sondergaard, 2011 (32)	52	$7{,}5 \cdot e^{10}$ UFC	8 weeks	AVS 0-100	Tendency to improve in TG vs CG
	Simren, 2010 (33)	67	$5 \cdot 10^7$ UFC/mL 200 mL 2 v/d	8 weeks	AVS 0-100	No differences in TG vs CG Improvements in TG‡ and in CG‡

Table 1. Effects of probiotics in abdominal pain treatment of IBS patients. *(Continued)*

Probiotic mixes	Study (ref.)	Nº of patients	Dosage	Treatment duration	Pain measurement scale	Results
B. longum LA 101, *Lb. acidophilus* LA 102, *L. lactis* LA 103, *S. thermophilus* LA 104	Drouault-Holowacz, 2008 (40)	100	$1 \cdot 10^{10}$ UFC	4 weeks	AVS 0-10	Tendency to improve TG vs CG Improvement in TG‡ and in CG‡
B. bifidum (KCTC 12 199BP), *B. lactis* (KCTC 11 904BP), *B. longum* (KCTC 12 200BP), *L. acidophilus* (KCTC 11 906BP), *L. rhamnosus* (KCTC 12 202BP), *S. thermophilus* (KCTC 11 870BP)	Yoon, 2014 (18)	49	$5 \cdot 10^{9}$ UFC 500 mg 2 v/d	4 weeks	Scale 0-10	Tendency to improve in TG vs CG Improvements in TG‡
L. rhamnosus GG (ATCC 53103, LGG), *L. rhamnosus* Lc705 (DSM 7061), *P. freudenreichii* ssp. *Shermanii JS* (DSM 7067), *B. animalis* ssp. *lactis* Bb12 (DSM 15954)	Kajander, 2008 (15)	71	$1 \cdot 10^{7}$ UFC/mL 1.2 dL	5 months	Scale 0-4	Tendency to improve in TG vs CG
L. rhamnosus GG, *L. rhamnosus* LC705, *B breve* Bb99, *P. freudenreichii* ssp. *Shermanii* JS	Kajander, 2005 (46)	86	$8\text{-}9 \cdot 10^{9}$ UFC	6 months	Scale 0-4	Tendency to improve in TG vs CG
L. acidophilus CUL-60 (NCIMB 30157) y CUL-21 (NCIMB 30156), *B. bifidum* CUL-20 (NCIMB 30153), *B. lactis* CUL-34 (NCIMB 30172)	Williams, 2009 (37)	52	$2.5 \cdot 10^{10}$ UFC	8 weeks	AVS 0-100	No differences in TG vs CG Improvements in TG‡ and in CG‡
VSL#3: *B. longum, B. infantis, B. breve, L. acidophilus, L. casei, L. delbrueckii* ssp. *Bulgaricus, L. plantarum, S. salivarius* ssp. *thermophilus*	Michail, 2011 (10)	24	$9 \cdot 10^{8}$ UFC	8 weeks	Scale 0-3	No differences in TG vs CG
	Kim, 2005 (45)	48	#	8 weeks	AVS 0-100	
	Kim, 2003 (48)	59	#	8 weeks	AVS 0-100	
L. acidophilus KCTC 11906BP, *L. plantarum* KCTC11867BP, *L. rhamnosus* KCTC 11868BP, *B. breve* KCTC 11858BP, *B. lactis* KCTC 11903BP, *B. longum* KCTC 11860BP and *S. thermophilus* KCTC 11870BP	Ki Cha, 2012 (13)	47	$1 \cdot 10^{10}$ UFC	8 weeks	AVS 0-10	No differences in TG vs CG
L. sp. HY7801, *B. longum* HY8004, *L. brevis* HY7401	Hong, 2011 (31)	73	$4 \cdot 10^{9}$ UFC 3 v/d	8 weeks	Not indicated	No differences in TG vs CG
S. thermophilus, L. bulgaricus, L. acidophilus, B. longum	Zeng, 2008 (39)	29	$1 \cdot 10^{7}$ UFC/mL≈ 200 g	4 weeks	AVS 0-100	Improvements in TG‡

CG: control group; AVS: Analog visual scale; TG: treatment group; t/d: times/day.
≈ $1 \cdot 10^{8}$ cfu/ml of *S. thermophilus*.
¶ $1{,}25 \times 10^{10}$ cfu of *B. Lactis* and $1{,}2 \times 10^{9}$ cfu of *S. thermophilus* and *L. burgaricus*.
# 450 billion lyophilized cells.
¥ Patients treated with 1×10^{8} live bacterial cells
* Improvements for weeks 1,2,4,5 and 7 of the treatment and for week 1 of the follow-up period.
§ Improvement for weeks 2 and 7 of the treatment.
‡ When compared to the results of the initial data.

from a group treated with placebos (50). In this case, both the probiotic group and the placebo group showed improvements over pretreatment data for each group.

Lactobacillus salivarius ssp. *salivarius* UCC4331 strain improved abdominal pain in weeks 2 and 7 of the treatment but not at the end of the 8 week study (57). A study of administration of the *Escherichia coli Nissle 1917* strain showed improvements in abdominal pain at the beginning of the treatment in both the treatment group and the placebo group (40). There was also an increase in the visceral sensitivity threshold when this strain was administered to rats with post-inflammatory visceral hyperglasia, but not when it was administered to healthy rats (68).

Other clinical studies have looked at the actions of other individual probiotic strains but have found no significant differences in abdominal pain relief. These strains are *Saccharomyces boulardii* (41,42), *Bacillus coagulans* GBI-30 6086 (47), *Lactobacillus reuteri ATCC 55730* (60) and Lactobacillus casei rhamnosus LCR35 (38). In healthy rats, the *Lactobacillus rhamnosus* JB-1 strain* decreased visceral hypersensitivity in colorectal and gastric distention. The study showed that this effect has an impact on the dorsal root ganglia at a medullar level by preventing hyper excitability prior to a painful stimulus (65, 69, 70).

PROBIOTIC MIXES

Agrawal et al. have found that the mixture of *Bifidobacterium lactis* DN-173 010, *Streptococcus thermophilus*, and *Lactobacillus bulgaricus* has a positive effect on abdominal pain relief (51). They also found a correlation between abdominal distension and the colonic and oral-fecal transit times when patients were treated with this mix. However, the authors did not provide data regarding the correlation between abdominal pain and transit time. It might be possible that improvements in the distension observed in these patients could be, at least partially, responsible for alleviation of their abdominal pain. Two other studies of the same probiotic mix found improvements in both groups when comparing the results with the data at the beginning of the study (37, 55).

The following probiotic mixes have shown significant effects relieving pain for IBS patients:

1. *B. bifidum* BGN4, *B. lactis* AD011, *Lactobacillus acidophilus* AD031, and *Lactobacillus casei* IBS41 (49).
2. *L. acidophilus* SDC 2012 and 2013. In animal studies, Rousseaux et al. have shown decreased visceral pain when inducing opioid and cannabinoid receptors in epithelial rat cells after administering *L. acidophilus* NCFM (54, 71).

A study that evaluated the mix of *L. bulgaricus*, *S. thermophilus*, *Lactobacillus paracasei* ssp. *paracasei* F19, *L. acidophilus* La5, and *B. lactis* Bb12 found a tendency toward abdominal pain relief (45), but the authors did not provide any data on the value of p. Another study of the same probiotic mix showed no differences between groups (46), but there both the treatment group and the placebo group had decreased intestinal pain and less frequent pain at the beginning of the study.

The following probiotic mixes have shown tendencies to improve abdominal pain in IBS patients:

1. *Bifidobacterium longum* LA 101, *L. acidophilus* LA 102, *L. lactis* LA 103, and *S. thermophilus* LA 104 (p=0.054) (53). Improvements were found both in the treatment and the placebo group at the beginning of the study for all patients as well as each of the subgroups of IBS patients. In the subgroup of patients with an alternating pattern, significant relief of abdominal pain was found in both groups.
2. *B. bifidum* KCTC 12 199BP, *B. lactis* KCTC 11 904BP, *B. longum* KCTC 12 200BP, *L. acidophilus* KCTC 11 906BP, *L. rhamnosus* KCTC 12 202BP, and *S. thermophilus* KCTC 11 870BP (p=0.07) (30).
3. *L. rhamnosus* GG (ATCC 53103, LGG), *L. rhamnosus* Lc705 (DSM 7061), *Propionibacterium freudenreichii* ssp. *shermanii* JS (DSM 7067), and *B. animalis* ssp. *lactis* Bb12 (DSM 15954) (p=0.052) (27).
4. *Lactobacillus rhamnosus* GG, *L. rhamnosus* LC705, *Bifidobacterium breve* Bb99, and *P. freudenreichii* ssp. *shermanii* JS (p=0.110) (59).

The following probiotic mixes have shown no significant pain relief for patients with IBS (See table 1):

1. *L. acidophilus* CUL-60 (NCIMB 30157) and CUL-21 (NCIMB 30156), *B. bifidum* CUL-20 (NCIMB 30153), and *B. lactis* CUL-34 (NCIMB 30172) (50). In this study there was an improvement at the beginning of the study for the group treated with the probiotic, and abdominal pain relief as well as days with pain for the control group.
2. VSL#3 (*B. longum*, *B. infantis*, *B. breve*, *L. acidophilus*, *L. casei*, *L. delbrueckii ssp. Bulgaricus*, *L. plantarum*, S. salivarius ssp. *thermophilus*) (22,58,61). However, Dai et al. found decreased visceral hypersensitivity upon administering this probiotic mix in a rat model that simulate IBS with predominant diarrhea (72). These authors suggest that the antinoceptive effect of VSL#3 could be mediated in part by the empowerment of nitric oxide synthesis. That study also found decreased paracellular

* Although in the titles and articles the species L. reuterii are discussed, the authors corrected the name of the species (see reference 65 for details).

permeability and increased numbers of proteins involved in tight membrane junctions after administration of the probiotic. The authors found no relation between the inhibition of nitric oxide synthesis and the changes observed in intestinal permeability for which reason they postulate that there is no correlation between these factors. Distrutti et al. have also found that administration of VSL#3 to rats with visceral hypersensitivity and allodynia has an antinociceptive effect. They also found a reversion in the expression of genes that measure pain and inflammation (73). It also seems that this effect is not due to a change in the state of consciousness or to modification of the tone of the colon.

3. *L. acidophilus* KCTC 11906BP, *L. plantarum* KCTC11867BP, *L. rhamnosus* KCTC 11868BP, *B. breve* KCTC 11858BP, *B. lactis* KCTC 11903BP, *B. longum* KCTC 11860BP and *S. thermophilus* KCTC 11870BP (25).
4. *Lactobacillus* sp. HY7801, *B. longum* HY8004, and *L. brevis* HY7401 (44).

Zeng et al.(52) found that abdominal pain decreased in group of patients to whom a probiotic mix of *S., L. bulgaricus*, *L. acidophilus* and *B. longum* was administered while there was no improvement in the placebo group in a comparison of before and after data for each of the groups individually. However, the study did not show data comparing the two groups. They also suggest that the decreased permeability of the small intestine found after ingestion of the probiotic mix could partially explain alleviation of IBS symptoms including pain. However, no correlation analysis was provided nor was any significant difference between the probiotic and placebo groups shown.

Other animal studies have shown antinociceptive effects for various probiotic strains. Administration of the *Lactobacillus paracasei* NCC2461 strain has been found to modulate visceral hypersensitivity in mice with hypersensitivity induced by antibiotics in one study, and in two rat models with stress induced hypersensitivity (74, 75). The study of mice also found that the probiotic normalized levels of substance P. The study of rats also found that after administration of the probiotic intestinal permeability normalized in rats subject to maternal separation. These effects were specific to the probiotic strain employed since no effect was found after administration of *B. lactis* NCC362 or *Lactobacillus johnsonii* NCC533. A mix of another strain of *B. lactis* – CNCM I-2494– with *Lactococcus lactis* CNCM I-1631, *L. bulgaricus* and *S. thermophilus* decreased visceral sensitivity of mice subject to stress (76). It was also shown that this effect was dosage dependent. The authors of this study found normalization of paracellular permeability which suggests that it could be one of the factors that explain this antinociceptive effect.

Ait-Belgnaoui et al. have found that administration of the *Lactobacillus farciminis* CIP 103136 probiotic to stressed induced rats has an antinociceptive effect and increases colonic paracellular permeability (77). The release of nitric oxide by the probiotic could have influenced both of these factors. The probiotic may act to modulate intestinal permeability by preventing phosphorylation of the myosin light chain. The contraction of the cytoskeletons of the epithelial cells may lead to an opening of the tight junctions. This could be due to the presence of nitric oxide. However, as mentioned previously, other authors have not found a relation between increased paracellular permeability and the inhibition of nitric oxide synthesis after administration of the VSL#3 probiotic mix (72). A later study in which *Lactobacillus farciminis* CIP 103136 strain was administered to stressed induced rats observed decreased visceral hypersensitivity through the visceral nociceptive process at the spinal and supraspinal levels and also found decreasing over-expression of Fos proteins at these levels (78).

NEW PERSPECTIVES FOR STUDYING THE EFFECT OF PROBIOTICS IN ABDOMINAL PAIN RELIEF

It is currently accepted that communication between the central nervous system and the gastrointestinal tract is bidirectional, and it has furthermore been postulated that IBS is a multifactorial entity which includes deregulation of the gut-brain axis. To understand the action mechanism of probiotics in abdominal pain relief it will be necessary to clarify the effect of probiotics with antinociceptive effects on the regulation of this axis. Nevertheless, as this review has shown, there has been great progress in this field in the last 10 years.

Future research could look at the effect of certain probiotics in the regulation of different substances, cells and processes that have been found to be correlated to abdominal pain. These include the mastocytes (81-83), the nerve fibers of transient receptor potential vanilloid 1 (84, 85), serotonin (86), brain-derived neurotrophic factor (87), intestinal permeability (88), tight junction union proteins (86, 90), and cellular adhesion (91).

A correlation between abdominal pain and decreased numbers of tight junction JAM-A proteins and occlusion has been found in IBS patients (89, 90). Since probiotic treatment of animals produces decreased visceral hypersensitivity accompanied by reestablishment of tight junction protein levels, this could be one of the factors that explains the action mechanism of probiotics' antinociceptive effect (72-76).

Other possibilities for research include studying the effects of taking probiotics on patients with IBS and how these effects are related to abdominal pain. Among these effects are decreased permeability of the small intestine and normalization of the immune response (52, 57). Finally, the chronicity of abdominal pain makes it necessary to study the effects of probiotics on the central neural mechanism and psychological factors which may be related to modulation of abdominal pain (79, 92-94). The first steps are already being taken in this direction (70, 78).

A series of probiotic strains including *L. plantarum* DSM 9843 (299v)*, B. infantis* 35624 *and B. bifidum* MIMBb75 and three mixes of probiotics (*B. lactis* DN-173 010, *S. thermophilus* and *L. bulgaricus*; *B. bifidum* BGN4, *B. lactis* AD011, *L. acidophilus* AD031 and *L. casei* IBS41, and *L. acidophilus* SDC 2012 and 2013) have shown apparent antinociceptive effects and apparent abdominal pain relief in certain subgroups of patients with IBS. Perhaps, in the not so distant future they will be used to develop master formulas to treat this serious symptom which afflicts some patients with this functional disorder.

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