Review Article

Gut-Microbiota-Brain Axis and Its Effect on Neuropsychiatric Disorders With Suspected Immune Dysregulation

Anastasia I. Petra, MD[1]; Smaro Panagiotidou, MA[1]; Erifili Hatziagelaki, MD[2]; Julia M. Stewart, RB[1]; Pio Conti, DSc[3]; and Theoharis C. Theoharides, MS, PhD, MD[1,4,5]

[1]Molecular Immunopharmacology and Drug Discovery Laboratory, Department of Integrative Physiology and Pathobiology, Tufts University School of Medicine, Boston, Massachusetts; [2]Second Department of Internal Medicine, Attikon General Hospital, Athens Medical School, Athens, Greece; [3]Department of Medical Sciences, Immunology Division, University of Chieti, Via dei Vestini, Chieti, Italy; [4]Department of Internal Medicine, Tufts University School of Medicine and Tufts Medical Center, Boston, Massachusetts; and [5]Department of Psychiatry, Tufts University School of Medicine and Tufts Medical Center, Boston, Massachusetts

ABSTRACT

Purpose: Gut microbiota regulate intestinal function and health. However, mounting evidence indicates that they can also influence the immune and nervous systems and vice versa. This article reviews the bidirectional relationship between the gut microbiota and the brain, termed the microbiota-gut-brain (MGB) axis, and discusses how it contributes to the pathogenesis of certain disorders that may involve brain inflammation.

Methods: Articles were identified with a search of Medline (starting in 1980) by using the key words *anxiety, attention-deficit hypersensitivity disorder (ADHD), autism, cytokines, depression, gut, hypothalamic–pituitary–adrenal (HPA) axis, inflammation, immune system, microbiota, nervous system, neurologic, neurotransmitters, neuroimmune conditions, psychiatric, and stress*.

Findings: Various afferent or efferent pathways are involved in the MGB axis. Antibiotics, environmental and infectious agents, intestinal neurotransmitters/neuromodulators, sensory vagal fibers, cytokines, and essential metabolites all convey information to the central nervous system about the intestinal state. Conversely, the hypothalamic–pituitary–adrenal axis, the central nervous system regulatory areas of satiety, and neuropeptides released from sensory nerve fibers affect the gut microbiota composition directly or through nutrient availability. Such interactions seem to influence the pathogenesis of a number of disorders in which inflammation is implicated, such as mood disorder, autism-spectrum disorders, attention-deficit hypersensitivity disorder, multiple sclerosis, and obesity.

Implications: Recognition of the relationship between the MGB axis and the neuroimmune systems provides a novel approach for better understanding and management of these disorders. Appropriate preventive measures early in life or corrective measures such as use of psychobiotics, fecal microbiota transplantation, and flavonoids are discussed. (*Clin Ther*. 2015;37:984–995)

Key words: cytokines, gut, immune disorders, MGB axis, microbiota, nervous system diseases.

INTRODUCTION

Humans have up to 37% gene homology with bacteria and Archae.[1] Vast numbers of commensal micro-organisms reside on both the external and the internal surfaces of our bodies, especially the gut, outnumbering human somatic cells by ~10:1.[2] Our

Accepted for publication April 7, 2015.
http://dx.doi.org/10.1016/j.clinthera.2015.04.002
0149-2918/$ - see front matter

Table I. Beneficial functions of gut microbiota.

- Defense against pathogen colonization by nutrient competition and production of antimicrobial substances
- Fortification of intestinal epithelial barrier and induction of secretory immunoglobulin A synthesis to limit pathogenic bacteria penetration into tissues
- Facilitation of nutrient absorption by metabolizing indigestible dietary compounds
- Participation in the maturation and functionality of the host immune system by providing diverse signals for "tuning" the host immune status

colonization starts at birth during vaginal delivery with a maternal signature followed by complex "adult" microbiota after the first year of age.[3,4] As a result, the human body is considered a super-complex ecosystem, a social network with the gut microbiota having formed a permanent symbiotic relationship rather than a temporary form of parasitism.[5] Normally, the gastrointestinal (GI) microbiota has a symbiotic relationship with our enteric cells and contributes to basic physiological processes, including digestion, growth, and self-defense (Table I).

The present article reviews the bidirectional relationship between the gut microbiota and the brain, termed the microbiota-gut-brain (MGB) axis, and discusses how it contributes to the pathogenesis of certain disorders, that may involve brain inflammation.

MATERIALS AND METHODS

Articles were identified with a search of Medline (starting in 1980) by using the key words *anxiety, attention-deficit hypersensitivity disorder (ADHD), autism, cytokines, depression, gut, hypothalamic–pituitary–adrenal (HPA) axis, inflammation, immune system, microbiota, nervous system, neurologic, neurotransmitters, neuroimmune conditions, psychiatric, and stress*.

RESULTS

An individual's gut microbiota composition depends on the mode of delivery at birth, genetic predisposition, age, nutrition, physical activity, environmental factors, stress, infections, other diseases, and use of antibiotics. Brain function and psychological makeup are now increasingly considered to have a reciprocal relationship with the gut.[6] Disruption of the gut microbiota (dysbiosis) balance is known to contribute to, among others, the pathogenesis of GI diseases, particularly inflammatory bowel disorder (IBD)[7] and irritable bowel syndrome (IBS),[8] especially because the gut microbiome regulates immunity.[9–13] In fact, bacteria reportedly directly induce inflammation and pain.[14]

Accumulating evidence suggests that the gut microbiota maintain bidirectional interactions with critical parts of the central nervous system (CNS) and the immune system through direct and indirect pathways (Table II, Figure). These involve the endocrine (HPA axis), immune (chemokines, cytokines), autonomic nervous, and enteric nervous systems forming the MGB axis.[6]

Neuro/immune-active substances derived from the intestinal lumen can penetrate the gut mucosa, be transported by blood, cross the blood–brain barrier (BBB), and affect the CNS.[15] Gut microbiota can influence CNS function through their ability to synthesize or mimic a range of host-signaling neuroactive molecules, such as acetylcholine, catecholamines, γ-aminobutyric acid, histamine, melatonin, and 5-hydroxytryptamine (5-HT [serotonin]).[16] 5-HT is crucial in the regulation of peristalsis or modulation of sensation.[17]

Conversely, the composition of gut microbiota is influenced by emotional and physiologic stress.[18] One study found that healthy students during an extremely stressful time had fewer *Lactobacilli* present in their stool compared with less stressful periods.[19] Maternal separation stress between 6 and 9 months of age in rhesus monkeys resulted in decreased fecal *Lactobacilli* levels.[20] Exposure to chronic stress in adult mice decreased the relative abundance of *Bacteroides* species and increased the *Clostridium* species in the cecum; moreover, it caused activation of the immune system as documented by increased interleukin-6 and C-C chemokine ligand 2 production.[21] Acute stress increased GI[22,23] and BBB[24] permeability through activation of mast cells (MCs), which express high-affinity receptors for corticotropin-releasing hormone (CRH).[25] Moreover, chronic stress disrupted the intestinal barrier through MC activation and permitted penetration of luminal antigens, microflora

Table II. Pathways involved in bidirectional communication between gut microbiota, the brain, and the immune system.

Pathway	Effect
Afferent arm	
Change of the gut microbiota due to usage of antibiotics/infectious agents/probiotic bacteria	Alteration in the circulating levels of pro/anti-inflammatory cytokines that affect brain function
Modulation of various host metabolic reactions	Production of essential metabolites (eg, bile acids, choline, short-chain fatty acids)
Generation of neurotransmitters or neuromodulators in the intestinal lumen	Induction of epithelial cell release of molecules that stimulate afferent axons
Changes in tryptophan metabolism	Effects on behavior
Activation of sensory vagal fibers	Conveyance of information about the state of intestine to the CNS
Efferent arm	
HPA axis activation	Regulation of immune cells locally in the gut and systematically affecting gut permeability, motility, secretion, barrier function, and gut microbiota composition
Anti-inflammatory cholinergic reflex and/or sympathetic activation	Release of neurotransmitters that may affect gut microbiota composition, intestinal permeability, and local immunity
Activation of CNS regulatory areas of satiety	Impact on nutrient availability to intestinal microbiota and their composition

CNS = central nervous system; HPA = hypothalamic–pituitary–adrenal.

metabolites, toxins, and lipopolysaccharide into the systemic circulation and the CNS.[26] In fact, stress-induced MC activation has been implicated in functional GI diseases.[27] Maternal separation stress in mice also increased intestinal MC–neuron communication.[28]

MCs communicate with pathogens[29] and have been invoked as key modulatory cells in innate immunity,[30] as well as in inflammation[31–34] and autoimmunity.[35] A new finding concerning MCs is their ability to extracellularly secrete mitochondrial components, including DNA.[36] These components are then misconstrued by the body as "innate pathogens" and induce a strong auto-inflammatory response, leading to inflammation and neuronal damage.[37] The microbiota can modulate the immune system through other mechanisms.[38] In addition, the increased use of antibiotics results in depletion of microbiota-derived metabolites, impairs immune homeostasis, and contributes to chronic inflammation.[39]

Mood Disorders

Genes involved in synapse formation between neurons in the brain and neurons in the GI tract are similar, and any mutation could possibly lead to both brain and GI abnormalities.[40] Recent studies analyzing the human genome in brains from diseased subjects with psychiatric disorders reported only 2 clusters of affected genes with: (1) increased inflammation; and (2) decreased mitochondrial function.[41] Depression is associated with increased inflammatory biomarkers, such as interleukin-6, tumor necrosis factor-α, and C-reactive protein.[42] Schizophrenia has been linked to intestinal inflammation[43] and gastrojejunal ulcers.[44]

When ingested, "psychobiotics," which are live organisms, may produce health benefits in patients experiencing mood disorders.[45] In a study of 124 healthy volunteers (mean age, 61.8 years), those who consumed a mix of specific psychobiotics (*Lactobacillus helveticus*

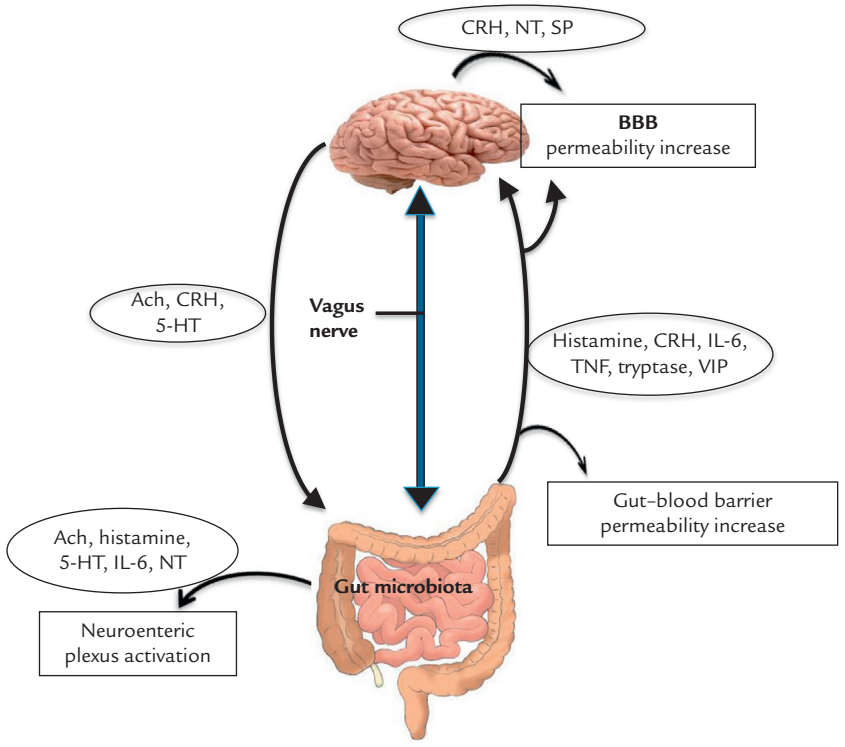

Figure. Diagrammatic representation of the microbiota–gut–brain (MGB) axis highlighting the proposed bidirectional communications. Gut microbiota can release molecules that may activate the neuroenteric plexus and stimulate brain production of neuropeptides, as well as increase gut–blood barrier and blood–brain barrier (BBB) permeability. The brain releases molecules that stimulate the neuroenteric plexus and gut function. The vagus nerve sends orthodromic and antidromic. CRH = corticotropin-releasing hormone; NT = neurotensin; SP = substance P; Ach = acetylcholine; IL-6 = interleukin 6; TNF = tumor necrosis factor; VIP = vasoactive intestinal peptide; 5-HT = 5-hydroxytryptamine.

and *Bifidobacterium longum*) exhibited less anxiety and depression.[19] Symptoms of "depression" were reported to decrease after probiotic treatment in the rat.[46] Additional studies showed beneficial effects of probiotics in animal models with altered behavioral phenotypes, as they reduced vagal-dependent activation of γ-aminobutyric acid receptors in response to physical and psychological stress.[46–51]

Studies in animals found that certain bacterial species could reduce mood changes. For instance, when *Citrobacter rodentium* was administered orally to CF-1 mice, there was an increase in anxious-like behavior 7 to 8 hours after the infection, through activation of vagal pathways.[52] Postnatal colonization of germ-free mice by orally feeding them different probiotics programmed the HPA for a stress response; for instance, when *Campylobacter jejuni* was given orally, it increased anxious-like behavior 7 hours after the infection.[53] Furthermore, a corresponding increase in brain-derived neurotrophic factor in the hippocampus and amygdala was evident and was eliminated after administration of antibiotic therapy in the mice. Of note, brain-derived neurotrophic factor is involved in the pathology of depression[54] and autism spectrum disorders (ASDs),[55] and it is also considered a biomarker for gastric hypersensitivity.[56]

Attention-Deficit Hypersensitivity Disorder and ASDs

ADHD is a neurodevelopmental disorder characterized by lack of attention, impulsiveness, and hyperactivity. Its cause is considered multifactorial, involving genetic predisposition, somatic mutations,

epigenetic changes, and perinatal factors (eg, low birth weight, prematurity, prenatal exposure to alcohol and/or smoke), as well as environmental and socioeconomic factors.[57]

Increasing evidence from clinical and epidemiologic studies suggests that children and adults with food allergies, eczema, or asthma have associated behavioral problems and neuropsychiatric disorders, including ADHD.[58–63] The gut microbiota are known to participate in susceptibility to allergies,[64,65] especially food allergens.[66] One meta-analysis reported that the Kaiser-Permanente diet using elimination of salicylates, artificial food colors and flavors, and the preservative butylated hydroxytoluene could decrease the hyperactivity of children with ADHD.[57] Children with ADHD substantially improved on either a diet free of artificial food colors[67] or by dietary supplementations with polyunsaturated fatty acids, iron, and zinc.[68] In fact, levels of these fatty acids in the plasma of ADHD children are reportedly low.[69] Food-based treatments in children with allergic disorders have been shown to significantly reduce ADHD-like behavior.[70]

ASDs are neurodevelopmental disorders characterized by deficits in social interactions and communication, along with repetitive and stereotyped behaviors.[71] Many children with ASDs present with GI symptoms[72–74] and altered GI flora.[71] Increasing evidence indicates that ASD pathogenesis may involve brain inflammation,[75] especially activation of microglia.[76,77] Moreover, ~30% of children with ASDs have autoantibodies against brain proteins,[78] and the presence of such antibodies has been strongly correlated with allergic symptoms.[79]

We recently showed that levels of the neuropeptide neurotensin, found both in the brain and the gut and CRH, were increased in the serum of children with ASDs; moreover, neuropeptide neurotensin was significantly correlated with the presence of GI symptoms.[80] We also reported elevated levels of mitochondrial DNA in the serum of children with ASDs,[81] and CRH has been shown to augment the stimulatory effect of mitochondrial DNA on MCs.[82] A recent article reported increased amounts of mitochondrial DNA in peripheral mononuclear cells from patients with ASDs.[83] Extracellular mitochondrial DNA could derive either from MCs, peripheral mononuclear cells, intestinal cells, or bacteria and is misconstrued as "innate pathogens," which lead to autoinflammatory reactions.[84]

Approximately 30% of children with ASDs are characterized by hyperserotonemia,[85] and a serotonin reuptake transporter gene mutation (*SERT Ala56*) was identified in some ASD children with hyperserotenemia.[86] Introduction of this mutation in mice resulted in communication delays and repetitive behaviors similar to those in children with ASDs. In fact, 5-HT can affect the immune system,[28] and autoimmune neuroinflammation was treated with a tryptophan metabolite.[87] The *SERT Ala56* mice were also constipated and had bacterial intestinal overgrowth similar to what is often seen in children with ASDs.[88]

Increased intestinal permeability would permit bacterial products, cytokines, and chemokines to enter the circulation and cross the BBB,[89] influencing brain and behavior. For example, children with ASDs had higher levels of immunoglobulins (A, G, and M) against cow's milk–derived allergens, and milk intake by these patients significantly worsened some of their behavioral symptoms.[70] Elimination of casomorphin, gliadorphin, colorings, sweeteners, and preservatives led to significant benefit. The gut microbiota composition appears to differ between healthy children and those with ASDs.[71] For example, there was a higher prevalence of *Bifidobacteria* in healthy control subjects compared with patients with ASDs.[90] In contrast, *Bacteroides vulgatus* and *Desulfovibrio* species were more commonly found in stools of children with ASDs; however, only *Desulfovibrio desulfuricans, Desulfovibrio fairfieldensis*, and *Desulfovibrio piger* were associated with regressive ASD. *Clostridium* species were increased at the expense of *Bifidobacterium* in ASD children with food allergies and pediatric IBD compared with sex-matched control children.[91] Children with ASD treated with oral vancomycin had significant improvements in behavioral, cognitive, and GI symptoms.[92] (Similar findings are discussed in detail in another article (Bouie, in press) in this issue of *Clinical Therapeutics*.) Such findings have led to the gut–brain connections being proposed as targeted treatment of ASDs.[93]

Multiple Sclerosis and Neuromyelitis Optica

Multiple sclerosis is an autoimmune disease characterized by progressive demyelination and deterioration of neurologic function.[94,95] It has been suggested that gut microbiota may contribute to the pathogenesis of this disease.[96] One study showed that germ-free mice had delayed induction of experimental autoimmune encephalomyelitis (EAE), probably

due to the attenuation of Th17 and autoreactive B-cell responses. In another study, mice genetically predisposed to develop EAE spontaneously did not develop EAE when housed under germ-free conditions; however, this outcome was reversed upon colonization with conventional microbiota in adulthood. Even the presence of commensal microbiota promoted the induction of EAE in germ-free B6 mice due to decreased interferon-γ and interleukin-17 responses.[97] A high-fat diet was found to increase the severity of EAE in mice, whereas caloric restriction attenuated symptoms of EAE.[98]

Patients with neuromyelitis optica (NMO) have aquaporin (AQP) autoantibodies (AQP4-seropositive) against the optic nerve and spinal cord but also more antibodies against GI antigens than healthy control subjects.[99] Specifically, 37% of these patients had increased levels of antibodies against at least 1 of the following: gliadin, tissue transglutaminase, intrinsic factor, parietal cells, and *Saccharomyces cerevisiae* compared with 8% of healthy control subjects; anti-gliadin and anti–*S cerevisiae* antibodies were the most frequent in AQP4-seropositive NMO ($P = 0.01$ and $P < 0.05$, respectively). In addition, the AQP4-specific T cells in patients with NMO exhibited cross-reactivity to a protein of *Clostridium perfringens*, supporting a microbiota-related molecular mimicry process in NMO pathogenesis.[100] Multiple sclerosis[101] and EAE[102] are precipitated or worsened with stress, which is known to also affect the gut.[103] In fact, stress-induced gut alterations can impact the brain and behavior.[104]

Obesity

Obesity has been called a psychiatric disease[105] and is associated with depression[106] and other neuropsychiatric disorders.[43] Adipocytokines can influence both the brain and the gut,[105] and recent evidence suggests that gut microbiota influence energy balance and weight.[68] Increased energy harvesting from diet, regulation of biologically active fatty acid tissue composition, chronic low-grade endotoxemia, and modulation of gut-derived peptide secretion are some of the proposed routes that link gut microbiota with obesity.[107]

Gut microbiota may also contribute to low-grade inflammation in obesity.[108] Increased fat intake has been associated with increased serum levels of lipopolysaccharide in healthy humans[109] and in mice.[110] This endotoxin can potentially trigger Toll-like receptors in adipose or on pancreatic β cells, contributing to both insulin resistance and β-cell damage.[111,112] Experimental endotoxemia induced adipose inflammation and insulin resistance in lean human subjects.[113] Modulation of gut microbiota by using probiotics in obese mice was found to decrease high-fat diet–induced lipopolysaccharide endotoxemia, as well as systemic and liver inflammation.[110,111]

Many studies have produced contradictory results regarding the types of bacteria that predominate in obese subjects compared with lean subjects.[114–116] For instance, metabolically obese mice with mutated leptin gene had different microbiota than mice without the mutation.[114] The same researchers later reported altered gut microbiota composition (reduction of *Bacteroidetes* and increase of *Firmicutes* phyla) in obese human subjects compared with lean human subjects.[117] In contrast, other authors reported a higher proportion of *Bacteroidetes* in overweight and obese subjects.[118] These conflicting results may be due to the variable methods of analysis and to the different profile of subjects.

Gut microbiota can convert undigested carbohydrates into short-chain fatty acids, such as acetate, propionate, and butyrate. These fatty acids are able to bind and activate 2 G-protein–coupled receptors (GPR41 and GPR43) on gut epithelial cells, leading to secretion of peptide YY, which suppresses gut motility and retards intestinal transit.[107] An interesting finding is that propionate could induce an autistic-like phenotype in rats.[119] Modulation of gut microbiota may have therapeutic potential in the management of metabolic disorders.[120]

Treatment and Future Directions

Therapeutic modulation of gut microbiota, possibly by the use of prebiotics and probiotics, may be helpful in disorders involving disturbances of the MGB axis.[121] Prebiotics can benefit both intestinal mucosa and systemic immunity because they reach the large intestine nonhydrolyzed and stimulate the growth of beneficial intestinal microbiota.[122] Probiotics could restore intestinal permeability by improving the function of the mucosal barrier.[123] Administration of different probiotics has been reported to be beneficial in humans with abdominal pain[124,125] and increased the pain threshold in rats.[126] *Lactobacillus acidophilus* induced the expression of the cannabinoid 2 and μ-opioid 1 receptors in the colonic epithelium,[127] whereas *Lactobacillus farciminis* inhibited stress-induced

visceral hypersensitivity.[128] However, use of probiotics may result in both beneficial and detrimental effects. For example, there were beneficial effects in IBS with the use of probiotics *Bifidobacterium infantis* 35624[129,130] and *Bifidobacterium lactis and B animalis* DN173010[131] and of probiotic mixtures, such as *Escherichia coli* (DSM 17252) and *Enterococcus faecalis* (DSM 16440)[132] or *Lactobacillus rhamnosus* GG, *L rhamnosus* LC705, *Bifidobacterium breve* Bb99, and *Propionibacterium freudenreichii* species *shermanii* JS.[133,134] On the contrary, use of other probiotic mixtures, such as *Lactobacillus paracasei* species *Paracasei* F19, *L acidophilus* La5, and *Bifidobacterium lactis* Bb12[135,136] or *Lactobacillus plantarum* MF 1298,[137] had negative effects in IBS. Nonabsorbable antibiotics (eg, oral rifaximin) were shown to be beneficial in IBS.[138]

Natural flavonoids may be useful because they have immunoregulatory actions.[139] For instance, the quercetin glycoside rutin is cleaved by gut bacteria to liberate quercetin, which has anti-inflammatory actions.[140] Quercetin, luteolin, and tetramethoxyluteolin are potent inhibitors of MCs.[141]

Fecal microbiota transplantation from a healthy donor can re-establish intestinal flora balance and could be used for specific GI diseases,[142] especially the treatment of *Clostridium difficile* infection,[143] and it may possibly be efficacious in IBD.[144]

CONCLUSIONS

Gut microbiota were considered decremental to health and the focus had been on pathogenic species. Increasing evidence indicates that a delicate balance of gut microorganisms is necessary for health, disruption of which is associated especially with neuropsychiatric disorders. The gut-microbiota-brain axis involves active by-directional flow of information, which comprises of immune and neuroregulatory molecules, constitutes an exciting new field. In spite of numerous publications, proper gut microbiota balance cannot be achieved simply by introduction of probiotics requiring new treatment approaches.

ACKNOWLEDGMENTS

This study was partially funded by the National Institutes of Health (grants NS38326 and AR47652), as well as the Autism Collaborative, the Autism Research Institute, the National Autism Association, Safe Minds, the Johnson B. Johnson Foundation, the Michael and Margaret Johnson Family Foundation, The Nancy Lurie Marks Foundation, and Theta Biomedical Consulting and Development Co, Inc.

CONFLICTS OF INTEREST

Dr. Theoharides is the inventor of US patents No. 6,624,148; 6,689,748; 6,984,667, and EPO 1365777, which cover methods and compositions of MC blockers, including flavonoids, as well as US patents No. 7,906,153 and 8,268,365 for the treatment of brain inflammation. 13/009.282 for the diagnosis and treatment of ASDs. The authors have indicated that they have no other conflicts of interest regarding the content of this article.

REFERENCES

1. Fall-Ngai M, Hadfield MG, Bosch TC, et al. Animals in a bacterial world, a new imperative for the life sciences. *Proc Natl Acad Sci U S A*. 2013;110:3229–3236.
2. Belkaid Y, Naik S. Compartmentalized and systemic control of tissue immunity by commensals. *Nat Immunol*. 2013;14:646–653.
3. Grenham S, Clarke G, Cryan JF, Dinan TG. Brain-gut-microbe communication in health and disease. *Front Physiol*. 2011;2:94.
4. Palmer C, Bik EM, DiGiulio DB, et al. Development of the human infant intestinal microbiota. *PLoS Biol*. 2007;5:e177.
5. O'Hara AM, Shanahan F. The gut flora as a forgotten organ. *EMBO Rep*. 2006;7:688–693.
6. Mayer EA. Gut feelings: the emerging biology of gut-brain communication. *Nat Rev Neurosci*. 2011;12:453–466.
7. Li J, Butcher J, Mack D, Stintzi A. Functional impacts of the intestinal microbiome in the pathogenesis of inflammatory bowel disease. *Inflamm Bowel Dis*. 2014;21:139–153.
8. Lee KN, Lee OY. Intestinal microbiota in pathophysiology and management of irritable bowel syndrome. *World J Gastroenterol*. 2014;20:8886–8897.
9. Sternberg EM. Neural regulation of innate immunity: a coordinated nonspecific host response to pathogens. *Nat Rev Immunol*. 2006;6:318–328.
10. Maranduba CM, De Castro SB, de Souza GT, et al. Intestinal microbiota as modulators of the immune system and neuroimmune system: impact on the host health and homeostasis. *J Immunol Res*. 2015;2015:931574.
11. Salzman NH. The role of the microbiome in immune cell development. *Ann Allergy Asthma Immunol*. 2014;113:593–598.
12. Spasova DS, Surh CD. Blowing on embers: commensal microbiota and our immune system. *Front Immunol*. 2014;5:318.
13. Kumar R, Parsad D, Kanwar AJ. Role of apoptosis and melanocytorrhagy: a comparative study of melanocyte adhesion in stable and unstable vitiligo. *Br J Dermatol*. 2011;164:187–191.

14. Chiu IM, Heesters BA, Ghasemlou N, et al. Bacteria activate sensory neurons that modulate pain and inflammation. *Nature*. 2013;501:52–57.
15. Theoharides TC, Weinkauf C, Conti P. Brain cytokines and neuropsychiatric disorders. *J Clin Psychopharmacol*. 2004;24:577–581.
16. Barrett E, Ross RP, O'Toole PW, et al. Gamma-aminobutyric acid production by culturable bacteria from the human intestine. *J Appl Microbiol*. 2012;113:411–417.
17. Talley NJ. Serotoninergic neuroenteric modulators. *Lancet*. 2001;358:2061–2068.
18. Dinan TG, Cryan JF. Regulation of the stress response by the gut microbiota: implications for psychoneuroendocrinology. *Psychoneuroendocrinology*. 2012;37:1369–1378.
19. Dinan TG, Cryan JF. Melancholic microbes: a link between gut microbiota and depression? *Neurogastroenterol Motil*. 2013;25:713–719.
20. Bailey MT, Lubach GR, Coe CL. Prenatal stress alters bacterial colonization of the gut in infant monkeys. *J Pediatr Gastroenterol Nutr*. 2004;38:414–421.
21. Bailey MT, Dowd SE, Galley JD, et al. Exposure to a social stressor alters the structure of the intestinal microbiota: implications for stressor-induced immunomodulation. *Brain Behav Immun*. 2011;25:397–407.
22. Theoharides TC. irritable bowel syndrome and ulcerative colitis: mast cell numbers are increased, but activation is more important. *Dig Dis Sci*. 2014;59:897–898.
23. Overman EL, Rivier JE, Moeser AJ. CRF induces intestinal epithelial barrier injury via the release of mast cell proteases and TNF-alpha. *PloS One*. 2012;7:e39935.
24. Esposito P, Chandler N, Kandere-Grzybowska K, et al. Corticotropin-releasing hormone (CRH) and brain mast cells regulate blood-brain-barrier permeability induced by acute stress. *J Pharmacol Exp Ther*. 2002;303:1061–1066.
25. Cao J, Papadopoulou N, Kempuraj D, et al. Human mast cells express corticotropin-releasing hormone (CRH) receptors and CRH leads to selective secretion of vascular endothelial growth factor. *J Immunol*. 2005;174:7665–7675.
26. Santos J, Yang PC, Soderholm JD, et al. Role of mast cells in chronic stress induced colonic epithelial barrier dysfunction in the rat. *Gut*. 2001;48:630–636.
27. Rijnierse A, Nijkamp FP, Kraneveld AD. Mast cells and nerves tickle in the tummy: implications for inflammatory bowel disease and irritable bowel syndrome. *Pharmacol Ther*. 2007;116:207–235.
28. Idzko M, Panther E, Stratz C, et al. The serotoninergic receptors of human dendritic cells: identification and coupling to cytokine release. *J Immunol*. 2004;172:6011–6019.
29. Marshall JS. Mast-cell responses to pathogens. *Nat Rev Immunol*. 2004;4:787–799.
30. Galli SJ, Nakae S, Tsai M. Mast cells in the development of adaptive immune responses. *Nat Immunol*. 2005;6:135–142.
31. Theoharides TC, Alysandratos KD, Angelidou A, et al. Mast cells and inflammation. *Biochim Biophys Acta*. 2010;1822:21–33.
32. Kinet JP. The essential role of mast cells in orchestrating inflammation. *Immunol Rev*. 2007;217:5–7.
33. Sismanopoulos N, Delivanis DA, Alysandratos KD, et al. Mast cells in allergic and inflammatory diseases. *Curr Pharm Des*. 2012;18:2261–2277.
34. Galli SJ, Tsai M, Piliponsky AM. The development of allergic inflammation. *Nature*. 2008;454:445–454.
35. Rottem M, Mekori YA. Mast cells and autoimmunity. *Autoimmun Rev*. 2005;4:21–27.
36. Zhang B, Asadi S, Weng Z, et al. Stimulated human mast cells secrete mitochondrial components that have autocrine and paracrine inflammatory actions. *PloS One*. 2012;7:e49767.
37. Lauritzen KH, Moldestad O, Eide L, et al. Mitochondrial DNA toxicity in forebrain neurons causes apoptosis, neurodegeneration, and impaired behavior. *Mol Cell Biol*. 2010;30:1357–1367.
38. Kelly D, Mulder IE. Microbiome and immunological interactions. *Nutr Rev*. 2012;70(Suppl 1):S18–S30.
39. Lopez CA, Kingsbury DD, Velazquez EM, Baumler AJ. Collateral damage: microbiota-derived metabolites and immune function in the antibiotic era. *Cell Host Microbe*. 2014;16:156–163.
40. Hadhazy A. Think Twice: How the Gut's "Second Brain" Influences Mood and Well-Being. Scientific American, 2010. http://www.scientificamerican.com/article/gut-second-brain/.
41. Theoharides TC, Zhang B, Conti P. Decreased mitochondrial function and increased brain inflammation in bipolar disorder and other neuropsychiatric diseases. *J Clin Psychopharmacol*. 2011;31:685–687.
42. Miller AH, Maletic V, Raison CL. Inflammation and its discontents: the role of cytokines in the pathophysiology of major depression. *Biol Psychiatry*. 2009;65:732–741.
43. Severance EG, Alaedini A, Yang S, et al. Gastrointestinal inflammation and associated immune activation in schizophrenia. *Schizophr Res*. 2012;138:48–53.
44. Ozdemir V, Jamal MM, Osapay K, et al. Cosegregation of gastrointestinal ulcers and schizophrenia in a large national inpatient discharge database: revisiting the "brain-gut axis" hypothesis in ulcer pathogenesis. *J Investig Med*. 2007;55:315–320.
45. Dinan TG, Stanton C, Cryan JF. Psychobiotics: a novel class of psychotropic. *Biol Psychiatry*. 2013;74:720–726.
46. Desbonnet L, Garrett L, Clarke G, et al. The probiotic Bifidobacteria

infantis: an assessment of potential antidepressant properties in the rat. *J Psychiatr Res*. 2008;43:164–174.
47. Hsiao EY, McBride SW, Hsien S, et al. Microbiota modulate behavioral and physiological abnormalities associated with neurodevelopmental disorders. *Cell*. 2013;155:1451–1463.
48. Bravo JA, Forsythe P, Chew MV, et al. Ingestion of Lactobacillus strain regulates emotional behavior and central GABA receptor expression in a mouse via the vagus nerve. *Proc Natl Acad Sci U S A*. 2011;108:16050–16055.
49. Ait-Belgnaoui A, Durand H, Cartier C, et al. Prevention of gut leakiness by a probiotic treatment leads to attenuated HPA response to an acute psychological stress in rats. *Psychoneuroendocrinology*. 2012;37:1885–1895.
50. Bercik P, Park AJ, Sinclair D, et al. The anxiolytic effect of Bifidobacterium longum NCC3001 involves vagal pathways for gut-brain communication. *Neurogastroenterol Motil*. 2011;23:1132–1139.
51. Arseneault-Bréard J, Rondeau I, Gilbert K, et al. Combination of Lactobacillus helveticus R0052 and Bifidobacterium longum R0175 reduces post-myocardial infarction depression symptoms and restores intestinal permeability in a rat model. *Br J Nutr*. 2012;107:1793–1799.
52. Lyte M, Li W, Opitz N, et al. Induction of anxiety-like behavior in mice during the initial stages of infection with the agent of murine colonic hyperplasia Citrobacter rodentium. *Physiol Behav*. 2006;89:350–357.
53. Sudo N, Chida Y, Aiba Y, et al. Postnatal microbial colonization programs the hypothalamic-pituitary-adrenal system for stress response in mice. *J Physiol*. 2004;558(Pt 1):263–275.
54. Kotan Z, Sarandol E, Kirhan E, et al. Serum brain-derived neurotrophic factor, vascular endothelial growth factor and leptin levels in patients with a diagnosis of severe major depressive disorder with melancholic features. *Ther Adv Psychopharmacol*. 2012;2:65–74.
55. Theoharides TC, Athanassiou M, Panagiotidou S, Doyle R. Dysregulated brain immunity and neurotrophin signaling in Rett syndrome and autism spectrum disorders. *J Neuroimmunol*. 2015;279:33–38.
56. Winston JH, Sarna SK. Developmental origins of functional dyspepsia-like gastric hypersensitivity in rats. *Gastroenterology*. 2013;144:570–579.
57. Schab DW, Trinh NH. Do artificial food colors promote hyperactivity in children with hyperactive syndromes? A meta-analysis of double-blind placebo-controlled trials. *J Dev Behav Pediatr*. 2004;25:423–434.
58. Chang HY, Seo JH, Kim HY, et al. Allergic diseases in preschoolers are associated with psychological and behavioural problems. *Allergy Asthma Immunol Res*. 2013;5:315–321.
59. Genuneit J, Braig S, Brandt S, et al. Infant atopic eczema and subsequent attention-deficit/hyperactivity disorder—a prospective birth cohort study. *Pediatr Allergy Immunol*. 2014;25:51–56.
60. Tsai JD, Chang SN, Mou CH, et al. Association between atopic diseases and attention-deficit/hyperactivity disorder in childhood: a population-based case-control study. *Ann Epidemiol*. 2013;23:185–188.
61. Jedrychowski W, Maugeri U, Perera F, et al. Cognitive function of 6-year old children exposed to mold-contaminated homes in early postnatal period. Prospective birth cohort study in Poland. *Physiol Behav*. 2011;104:989–995.
62. Scahill L, Graft-Johnson A. Food allergies, asthma, and attention deficit hyperactivity disorder. *J Child Adolesc Psychiatr Nurs*. 1997;10:36–40.
63. Schmitt J, Romanos M, Schmitt NM, et al. Atopic eczema and attention-deficit/hyperactivity disorder in a population-based sample of children and adolescents. *JAMA*. 2009;301:724–726.
64. Abrahamsson TR, Wu RY, Jenmalm MC. Gut microbiota and allergy: the importance of the pregnancy period. *Pediatr Res*. 2015;77:214–219.
65. Kim BJ, Lee SY, Kim HB, et al. Environmental changes, microbiota, and allergic diseases. *Allergy Asthma Immunol Res*. 2014;6:389–400.
66. Cao S, Feehley TJ, Nagler CR. The role of commensal bacteria in the regulation of sensitization to food allergens. *FEBS Lett*. 2014;588:4258–4266.
67. Nigg JT, Lewis K, Edinger T, Falk M. Meta-analysis of attention-deficit/hyperactivity disorder or attention-deficit/hyperactivity disorder symptoms, restriction diet, and synthetic food color additives. *J Am Acad Child Adolesc Psychiatry*. 2012;51:86–97.
68. Murphy EF, Cotter PD, Healy S, et al. Composition and energy harvesting capacity of the gut microbiota: relationship to diet, obesity and time in mouse models. *Gut*. 2010;59:1635–1642.
69. Gillies D, Sinn JK, Lad SS, et al. Polyunsaturated fatty acids (PUFA) for attention deficit hyperactivity disorder (ADHD) in children and adolescents. *Cochrane Database Syst Rev*. 2012;7:CD007986.
70. de Theije CG, Bavelaar BM, Lopes da Silva S, et al. Food allergy and food-based therapies in neurodevelopmental disorders. *Pediatr Allergy Immunol*. 2014;25:218–226.
71. Finegold SM. State of the art; microbiology in health and disease. Intestinal bacterial flora in autism. *Anaerobe*. 2011;17:367–368.
72. Horvath K, Papadimitriou JC, Rabsztyn A, et al. Gastrointestinal abnormalities in children with autistic disorder. *J Pediatr*. 1999;135:559–563.
73. White JF. Intestinal pathophysiology in autism. *Exp Biol Med (Maywood)*. 2003;228:639–649.
74. Buie T, Campbell DB, Fuchs GJ III, et al. Evaluation, diagnosis, and

treatment of gastrointestinal disorders in individuals with ASDs: a consensus report. *Pediatrics*. 2010; 125(Suppl 1):S1–18.
75. Theoharides TC, Asadi S, Patel A. Focal brain inflammation and autism. *J Neuroinflammation*. 2013;10:46.
76. Zhan Y, Paolicelli RC, Sforazzini F, et al. Deficient neuron-microglia signaling results in impaired functional brain connectivity and social behavior. *Nat Neurosci*. 2014;17: 400–406.
77. Gupta S, Ellis SE, Ashar FN, et al. Transcriptome analysis reveals dysregulation of innate immune response genes and neuronal activity-dependent genes in autism. *Nat Commun*. 2014;5:5748.
78. Wills S, Cabanlit M, Bennett J, et al. Detection of autoantibodies to neural cells of the cerebellum in the plasma of subjects with autism spectrum disorders. *Brain Behav Immun*. 2008;23:64–74.
79. Mostafa GA, Al-Ayadhi LY. The possible relationship between allergic manifestations and elevated serum levels of brain specific autoantibodies in autistic children. *J Neuroimmunol*. 2013;261:77–81.
80. Tsilioni I, Dodman N, Petra AI, et al. Elevated serum neurotensin and CRH levels in children with autistic spectrum disorders and tail-chasing bull terriers with a phenotype similar to autism. *Transl Psychiatry*. 2014;4:e466.
81. Zhang B, Angelidou A, Alysandratos KD, et al. Mitochondrial DNA and anti-mitochondrial antibodies in serum of autistic children. *J Neuroinflammation*. 2010;7:80.
82. Asadi S, Theoharides TC. Corticotropin-releasing hormone and extracellular mitochondria augment IgE-stimulated human mast-cell vascular endothelial growth factor release, which is inhibited by luteolin. *J Neuroinflam*. 2012;9:85.
83. Chen S, Zongchang L, He Y, et al. Elevated mitochondrial DNA copy number in peripheral blood cells is associated with childhood autism. *BMC Psychiatry*. 2015;15:50.
84. Theoharides TC, Asadi S, Panagiotidou S, Weng Z. The "missing link" in autoimmunity and autism: extracellular mitochondrial components secreted from activated live mast cells. *Autoimmun Rev*. 2013;12:1136–1142.
85. Hranilovic D, Bujas-Petkovic Z, Tomicic M, et al. Hyperserotonemia in autism: activity of 5HT-associated platelet proteins. *J Neural Transm*. 2009;116:493–501.
86. Veenstra-Vanderweele J, Jessen TN, Thompson BJ, et al. Modeling rare gene variation to gain insight into the oldest biomarker in autism: construction of the serotonin transporter Gly56Ala knock-in mouse. *J Neurodev Disord*. 2009;1: 158–171.
87. Platten M, Ho PP, Youssef S, et al. Treatment of autoimmune neuroinflammation with a synthetic tryptophan metabolite. *Science*. 2005;310:850–855.
88. Kerr TM, Muller CL, Miah M, et al. Genetic background modulates phenotypes of serotonin transporter Ala56 knock-in mice. *Mol Autism*. 2013;4:35.
89. Banks WA, Erickson MA. The blood-brain barrier and immune function and dysfunction. *Neurobiol Dis*. 2010;37:26–32.
90. Finegold SM, Molitoris D, Song Y, et al. Gastrointestinal microflora studies in late-onset autism. *Clin Infect Dis*. 2002;35(Suppl 1):S6–S16.
91. Adams JB, Johansen LJ, Powell LD, et al. Gastrointestinal flora and gastrointestinal status in children with autism—comparisons to typical children and correlation with autism severity. *BMC Gastroenterol*. 2011;11:22.
92. Sandler RH, Finegold SM, Bolte ER, et al. Short-term benefit from oral vancomycin treatment of regressive-onset autism. *J Child Neurol*. 2000;15:429–435.
93. de Theije CG, Wu J, da Silva SL, et al. Pathways underlying the gut-to-brain connection in autism spectrum disorders as future targets for disease management. *Eur J Pharmacol*. 2011;668(Suppl 1):S70–S80.
94. Hemmer B, Kerschensteiner M, Korn T. Role of the innate and adaptive immune responses in the course of multiple sclerosis. *Lancet Neurol*. 2015;14:406–419.
95. Mahad DH, Trapp BD, Lassmann H. Pathological mechanisms in progressive multiple sclerosis. *Lancet Neurol*. 2015;14:183–193.
96. Berer K, Mues M, Koutrolos M, et al. Commensal microbiota and myelin autoantigen cooperate to trigger autoimmune demyelination. *Nature*. 2011;479:538–541.
97. Ochoa-Reparaz J, Mielcarz DW, Ditrio LE, et al. Role of gut commensal microflora in the development of experimental autoimmune encephalomyelitis. *J Immunol*. 2009; 183:6041–6050.
98. Piccio L, Stark JL, Cross AH. Chronic calorie restriction attenuates experimental autoimmune encephalomyelitis. *J Leukoc Biol*. 2008; 84:940–948.
99. Banati M, Csecsei P, Koszegi E, et al. Antibody response against gastrointestinal antigens in demyelinating diseases of the central nervous system. *Eur J Neurol*. 2013; 20:1492–1495.
100. Varrin-Doyer M, Spencer CM, Schulze-Topphoff U, et al. Aquaporin 4-specific T cells in neuromyelitis optica exhibit a Th17 bias and recognize Clostridium ABC transporter. *Ann Neurol*. 2012;72: 53–64.
101. Theoharides TC, Enakuaa S, Sismanopoulos N, et al. Contribution of stress to asthma worsening through mast cell activation. *Ann Allergy Asthma Immunol*. 2012;109:14–19.
102. Chandler N, Jacobson S, Connolly R, et al. Acute stress shortens the time of onset of experimental allergic encephalomyelitis (EAE) in SJL/J

mice. *Brain Behav Immun*. 2002;16:757–763.
103. Tache Y, Martinez V, Million M, Wang L. Stress and the gastrointestinal tract III. Stress-related alterations of gut motor function: role of brain corticotropin-releasing factor receptors. *Am J Physiol Gastrointest Liver Physiol*. 2001;280:G173–G177.
104. Gur TL, Worly BL, Bailey MT. Stress and the commensal microbiota: importance in parturition and infant neurodevelopment. *Front Psychiatry*. 2015;6:5.
105. Aguilar-Valles A, Inoue W, Rummel C, Luheshi GN. Obesity, adipokines and neuroinflammation. *Neuropharmacology*. 2015 Jan 15. [E-pub ahead of print].
106. Byrne ML, O'Brien-Simpson NM, Mitchell SA, Allen NB. Adolescent-onset depression: are obesity and inflammation developmental mechanisms or outcomes? *Child Psychiatry Hum Dev*. 2015 Feb 10. [E-pub ahead of print].
107. Musso G, Gambino R, Cassader M. Obesity, diabetes, and gut microbiota: the hygiene hypothesis expanded? *Diabetes Care*. 2010;33:2277–2284.
108. Manco M, Putignani L, Bottazzo GF. Gut microbiota, lipopolysaccharides, and innate immunity in the pathogenesis of obesity and cardiovascular risk. *Endocr Rev*. 2010;31:817–844.
109. Amar J, Burcelin R, Ruidavets JB, et al. Energy intake is associated with endotoxemia in apparently healthy men. *Am J Clin Nutr*. 2008;87:1219–1223.
110. Cani PD, Neyrinck AM, Fava F, et al. Selective increases of bifidobacteria in gut microflora improve high-fat-diet-induced diabetes in mice through a mechanism associated with endotoxaemia. *Diabetologia*. 2007;50:2374–2383.
111. Cani PD, Amar J, Iglesias MA, et al. Metabolic endotoxemia initiates obesity and insulin resistance. *Diabetes*. 2007;56:1761–1772.
112. Creely SJ, McTernan PG, Kusminski CM, et al. Lipopolysaccharide activates an innate immune system response in human adipose tissue in obesity and type 2 diabetes. *Am J Physiol Endocrinol Metab*. 2007;292:E740–E747.
113. Mehta NN, McGillicuddy FC, Anderson PD, et al. Experimental endotoxemia induces adipose inflammation and insulin resistance in humans. *Diabetes*. 2010;59:172–181.
114. Ley RE, Backhed F, Turnbaugh P, et al. Obesity alters gut microbial ecology. *Proc Natl Acad Sci U S A*. 2005;102:11070–11075.
115. Backhed F, Ding H, Wang T, et al. The gut microbiota as an environmental factor that regulates fat storage. *Proc Natl Acad Sci U S A*. 2004;101:15718–15723.
116. Lyra A, Lahtinen S, Tiihonen K, Ouwehand AC. Intestinal microbiota and overweight. *Benef Microbes*. 2010;1:407–421.
117. Ley RE, Turnbaugh PJ, Klein S, Gordon JI. Microbial ecology: human gut microbes associated with obesity. *Nature*. 2006;444:1022–1023.
118. Schwiertz A, Taras D, Schafer K, et al. Microbiota and SCFA in lean and overweight healthy subjects. *Obesity (Silver Spring)*. 2010;18:190–195.
119. Thomas RH, Meeking MM, Mepham JR, et al. The enteric bacterial metabolite propionic acid alters brain and plasma phospholipid molecular species: further development of a rodent model of autism spectrum disorders. *J Neuroinflammation*. 2012;9:153.
120. Erejuwa OO, Sulaiman SA, Ab Wahab MS. Modulation of gut microbiota in the management of metabolic disorders: the prospects and challenges. *Int J Mol Sci*. 2014;15:4158–4188.
121. Ianiro G, Bibbo S, Gasbarrini A, Cammarota G. Therapeutic modulation of gut microbiota: current clinical applications and future perspectives. *Curr Drug Targets*. 2014;15:762–770.
122. Langlands SJ, Hopkins MJ, Coleman N, Cummings JH. Prebiotic carbohydrates modify the mucosa associated microflora of the human large bowel. *Gut*. 2004;53:1610–1616.
123. Ramakrishna BS. Probiotic-induced changes in the intestinal epithelium: implications in gastrointestinal disease. *Trop Gastroenterol*. 2009;30:76–85.
124. Bercik P, Collins SM, Verdu EF. Microbes and the gut-brain axis. *Neurogastroenterol Motil*. 2012;24:405–413.
125. Clarke G, Cryan JF, Dinan TG, Quigley EM. Review article: probiotics for the treatment of irritable bowel syndrome—focus on lactic acid bacteria. *Aliment Pharmacol Ther*. 2012;35:403–413.
126. McKernan DP, Fitzgerald P, Dinan TG, Cryan JF. The probiotic Bifidobacterium infantis 35624 displays visceral antinociceptive effects in the rat. *Neurogastroenterol Motil*. 2010;22:1029–1035, e268.
127. Rousseaux C, Thuru X, Gelot A, et al. Lactobacillus acidophilus modulates intestinal pain and induces opioid and cannabinoid receptors. *Nat Med*. 2007;13:35–37.
128. Ait-Belgnaoui A, Han W, Lamine F, et al. Lactobacillus farciminis treatment suppresses stress induced visceral hypersensitivity: a possible action through interaction with epithelial cell cytoskeleton contraction. *Gut*. 2006;55:1090–1094.
129. Aroniadis OC, Brandt LJ. Fecal microbiota transplantation: past, present and future. *Curr Opin Gastroenterol*. 2013;29:79–84.
130. Whorwell PJ, Altringer L, Morel J, et al. Efficacy of an encapsulated probiotic Bifidobacterium infantis 35624 in women with irritable bowel syndrome. *Am J Gastroenterol*. 2006;101:1581–1590.
131. Guglielmetti S, Mora D, Gschwender M, Popp K. Randomised clinical trial: Bifidobacterium bifidum

MIMBb75 significantly alleviates irritable bowel syndrome and improves quality of life—a double-blind, placebo-controlled study. *Aliment Pharmacol Ther*. 2011;33:1123–1132.
132. Enck P, Zimmermann K, Menke G, et al. A mixture of *Escherichia coli* (DSM 17252) and *Enterococcus faecalis* (DSM 16440) for treatment of the irritable bowel syndrome–a randomized controlled trial with primary care physicians. *Neurogastroenterol Motil*. 2008;20:1103–1109.
133. Kajander K, Hatakka K, Poussa T, et al. A probiotic mixture alleviates symptoms in irritable bowel syndrome patients: a controlled 6-month intervention. *Aliment Pharmacol Ther*. 2005;22:387–394.
134. Kajander K, Krogius-Kurikka L, Rinttila T, et al. Effects of multispecies probiotic supplementation on intestinal microbiota in irritable bowel syndrome. *Aliment Pharmacol Ther*. 2007;26:463–473.
135. Sondergaard B, Olsson J, Ohlson K, et al. Effects of probiotic fermented milk on symptoms and intestinal flora in patients with irritable bowel syndrome: a randomized, placebo-controlled trial. *Scand J Gastroenterol*. 2011;46:663–672.
136. Simren M, Ohman L, Olsson J, et al. Clinical trial: the effects of a fermented milk containing three probiotic bacteria in patients with irritable bowel syndrome—a randomized, double-blind, controlled study. *Aliment Pharmacol Ther*. 2010;31:218–227.
137. Ligaarden SC, Axelsson L, Naterstad K, et al. A candidate probiotic with unfavourable effects in subjects with irritable bowel syndrome: a randomised controlled trial. *BMC Gastroenterol*. 2010;10:16.
138. Pimentel M, Lembo A, Chey WD, et al. Rifaximin therapy for patients with irritable bowel syndrome without constipation. *N Engl J Med*. 2011;364:22–32.
139. Gee JM, Johnson IT. Polyphenolic compounds: interactions with the gut and implications for human health. *Curr Med Chem*. 2001;8:1245–1255.
140. Mascaraque C, Aranda C, Ocon B, et al. Rutin has intestinal antiinflammatory effects in the CD4+ CD62L+ T cell transfer model of colitis. *Pharmacol Res*. 2014;90:48–57.
141. Weng Z, Patel A, Panagiotidou S, Theoharides TC. The novel flavone tetramethoxyluteolin is a potent inhibitor of human mast cells. *J Allergy Clin Immunol*. 2014;14:01574–01577.
142. Aroniadis OC, Brandt LJ. Intestinal microbiota and the efficacy of fecal microbiota transplantation in gastrointestinal disease. *Gastroenterol Hepatol (N Y)*. 2014;10:230–237.
143. van Nood E, Vrieze A, Nieuwdorp M, et al. Duodenal infusion of donor feces for recurrent Clostridium difficile. *N Engl J Med*. 2013;368:407–415.
144. Colman RJ, Rubin DT. Fecal microbiota transplantation as therapy for inflammatory bowel disease: a systematic review and meta-analysis. *J Crohns Colitis*. 2014;8:1569–1581.

Address correspondence to: Theoharis C. Theoharides, MS, PhD, MD, Molecular Immunopharmacology and Drug Discovery Laboratory, Department of Integrative Physiology and Pathobiology, Tufts University School of Medicine, 136 Harrison Avenue, Boston, MA 02111. E-mail: theoharis.theoharides@tufts.edu