

# Psychobiotics: A Novel Class of Psychotropic

Timothy G. Dinan, Catherine Stanton, and John F. Cryan

Here, we define a psychobiotic as a live organism that, when ingested in adequate amounts, produces a health benefit in patients suffering from psychiatric illness. As a class of probiotic, these bacteria are capable of producing and delivering neuroactive substances such as gamma-aminobutyric acid and serotonin, which act on the brain-gut axis. Preclinical evaluation in rodents suggests that certain psychobiotics possess antidepressant or anxiolytic activity. Effects may be mediated via the vagus nerve, spinal cord, or neuroendocrine systems. So far, psychobiotics have been most extensively studied in a liaison psychiatric setting in patients with irritable bowel syndrome, where positive benefits have been reported for a number of organisms including *Bifidobacterium infantis*. Evidence is emerging of benefits in alleviating symptoms of depression and in chronic fatigue syndrome. Such benefits may be related to the anti-inflammatory actions of certain psychobiotics and a capacity to reduce hypothalamic-pituitary-adrenal axis activity. Results from large scale placebo-controlled studies are awaited.

**Key Words:** Brain-gut axis, depression, microbiota, probiotics, psychobiotics, stress

In his review of 2012, Thomas Insel, Director of the National Institute of Mental Health, referred to recent studies on the microbiota as among the most important published in the year and concluded that "our bodies are .....a complex ecosystem in which human cells represent a paltry 10% of the population. But beyond the sheer numbers, we now know about the profound diversity of this ecosystem and striking individual differences. How these differences in our microbial world influence the development of brain and behavior will be one of the great frontiers of clinical neuroscience in the next decade" (1). There is certainly an expanding volume of evidence to support the view that cognitive and emotional processes can be altered by microbes acting through the brain-gut axis (2). That gut pathogens can influence our mental process is recognized by all, but the fact that some bacteria may have positive mental health benefits is only now emerging. The brain-gut axis provides bidirectional communication between the brain and the gut and includes the metabolically complex intestinal microbiota (3,4). In this review, we will focus on the communicating pathways between the gut microbiota and the brain and the manner in which certain bacteria may be used to treat central nervous system disorders such as depression.

## Probiotics

The term probiotic is derived from the Greek meaning for life and the first formal description of a probiotic was provided by Metchnikoff in 1908, based on his observation that individuals who lived in a certain region of Bulgaria had a longer life span than those in other parts of the country, a fact that he related to the regular consumption of a fermented milk product (5). Probiotics are currently defined as a live organism that, when ingested in adequate amounts, exerts a health benefit (6). The reality is that many bacteria are claimed to be probiotic but very few have been subjected to rigorous investigation. Furthermore,

there is increasing evidence that certain immune responses can be induced by dead probiotic microorganisms (7), which adds a further layer of complexity to the issue. We define a psychobiotic as a live organism that, when ingested in adequate amounts, produces a health benefit in patients suffering from psychiatric illness. Logan and Katzman (8) first proposed the use of probiotics as adjunct therapy in the management of depression. Recently, Lyte (9) argues that probiotics function mechanistically as delivery vehicles for neuroactive compounds and these probiotics have the potential to act as psychotropic agents. It is clear that a broad range of bacteria manufacture and secrete neurochemicals. Certain strains of *Lactobacillus* and *Bifidobacterium* secrete gamma-aminobutyric acid (GABA). This is the main inhibitory neurotransmitter in the brain regulating many physiological and psychological processes, with dysfunction in the system implicated in anxiety and depression (10). We have recently reported the ability of intestinally derived strains of lactobacilli and bifidobacteria to produce GABA from monosodium glutamate (11). It has been suggested that the microbially produced GABA in the gut may have an effect on the brain-gut axis and Roshchina (12) indicates that a subspecies of *Lactobacillus* is capable of producing acetylcholine, another essential neurotransmitter in the human brain.

Serotonin (5-HT) is a metabolite of the amino acid tryptophan and plays an important role in the regulation of a number of bodily functions including mood. It has been shown that the plasma serotonin levels of conventional mice are significantly higher than germ free (GF) mice, who have no intestinal microbiota (13), demonstrating the capacity of the microbiota to influence levels. Furthermore, oral ingestion of *Bifidobacterium infantis* (*B. infantis*) increased levels of the serotonin precursor, tryptophan, in the plasma of rats, suggesting that the strain may have potential as an antidepressant (14). *Escherichia*, *Bacillus*, and *Saccharomyces* produce norepinephrine. *Candida*, *Streptococcus*, *Escherichia*, and *Enterococcus* produce serotonin, while *Bacillus* and *Serratia* have the potential to produce dopamine (9).

Endocannabinoids are lipid molecules that act as neurotransmitters/neuromodulators in the brain, which contains specific receptors (15). These cell receptor sites also engage with  $\Delta^9$ -tetrahydrocannabinol, the active constituent of *Cannabis sativa*, more commonly known as cannabis, a plant long known for its psychotropic properties. The endocannabinoid system and the gut microbiota can impact on the development of obesity and related disorders (16). In addition, a *Lactobacillus acidophilus* strain modulates expression of cannabinoid receptors in the spinal cord (17).

Thus, a large array of essential neurotransmitters are produced by microbes, many of which are key players within the human

From the Alimentary Pharmabiotic Centre, University College Cork and Teagasc Moorepark, Cork, Ireland.

Address correspondence to Timothy G. Dinan, M.D., Ph.D., Cork University Hospital, Department of Psychiatry, College Road, Wilton, Cork, Ireland; E-mail: [t.dinan@ucc.ie](mailto:t.dinan@ucc.ie).

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intestinal microbiota. Those probiotics that are shown *in vitro* to produce neuroactive compounds and in animal studies show behavioral effects are worthy of testing for psychobiotic potential, especially in stress-related disorders such as depression and anxiety.

## Gut Microbiota

The gut microbiota is a complex metabolic ecosystem and when adults ingest probiotics, such bacteria usually transit the gut or transiently colonize rather than becoming a permanent feature (18). The adult gut is inhabited by  $10^{13}$  to  $10^{14}$  microorganisms, a figure thought to be at least 10 times greater than the number of human cells in our bodies with 150 times as many genes as our genome (19,20). The estimated species number varies greatly but it is generally accepted that the human microbiome consists of greater than 1000 species (19) and more than 7000 strains (20). It is an environment dominated by bacteria, mainly strict anaerobes, but also including viruses, protozoa, archaea, and fungi (21,22). The microbiome is largely defined by two bacterial phylotypes, *Bacteroidetes* and *Firmicutes*, with *Proteobacteria*, *Actinobacteria*, *Fusobacteria*, and *Verrucomicrobia* phyla present in relatively low amounts (23). Colonization of the infant gut commences at birth when delivery exposes the infant to a complex microbiota and its initial microbiome has a maternal signature (23,24). Existing data indicate that babies born by caesarean section develop a different microbiota with aberrant short-term immune responses and a greater long-term risk of developing immune diseases (25–27). Whether or not caesarean section impacts on subsequent mental health is unclear, though higher rates of obesity in such children have been established. The microbiome of unweaned infants is simple with high interindividual variability (28,29). The numbers and diversity of strict anaerobes increase as a result of diet and environment, and after 1 year of age, a complex adult-like microbiome is evident (30,31).

Despite a significant interpersonal variation in the enteric microbiota, there seems to be a balance that confers health benefits, and an alteration in beneficial bacteria can negatively influence the well being of the individual (32). Several factors may alter the microbiome, such as infection, disease, and diet (33). Turnbaugh *et al.* (34) showed that switching from a low-fat, polysaccharide-rich diet to a high-fat, high-sugar diet shifted the structure of the microbiota within a single day and changed the representation of metabolic pathways in the microbiome. Recent studies suggest that antipsychotics may also alter the microbiota (35). In rodents, olanzapine was found to reduce the levels of *Proteobacteria* and *Actinobacteria* by day 21 of treatment and there was also a trend for an increase in the *Firmicutes* levels. No analysis of other psychotropic agents on the microbiota has so far been published.

Homeostatic mechanisms within the microbiota become less effective in the elderly. It is clear that the microbiota diverges between those who age healthily and those whose health deteriorates with age (32). It is not known if alteration in the microbiota is associated with psychiatric illness such as depression. However, it has been established that early life stress, which is a risk factor for major depression in adulthood, induces changes in the microbiota (36,37). Prenatal stressors have been shown to alter the microbiome in rhesus monkeys by reducing the overall numbers of *Bifidobacteria* and *Lactobacilli* (38). Early life maternal separation causes a significant decrease in fecal

*Lactobacillus* numbers on day 3 postseparation and can induce long-term effects on the microbiome as shown by O'Mahony *et al.* (36).

## Microbiota, Immunity, and Depression

The development of the intestinal immune system is largely dependent upon exposure to microorganisms. The GF paradigm is based on the fact that the uterine environment is sterile during prenatal development and with surgical delivery replacing the normal vaginal delivery, the opportunity for postnatal colonization of the gut is eliminated once animals are maintained in a sterile environment. In GF animals, which are almost without immune activity, association with certain selected microorganisms has been shown to be effective in the generation of the complete repertoire of immune function (39). For example, colonization with the segmented filamentous bacterium restores full functioning of the B and T lymphocytes in the gut (40–42).

While multiple pathways exist for bacteria to communicate with their host, pattern recognition receptors (i.e., Toll-like receptors [TLRs]) on host cells play a pivotal role. Ten TLRs are present on cells of the innate immune system in man and recognize characteristic molecular patterns (43). These receptors are the gateway to the innate immune system and are a first step in the cascade leading to cytokine production. They are also universally distributed on neurons (44), thus allowing them to respond to bacterial and viral components. While the intestinal epithelium acts largely as a barrier to translocation of microorganisms into the internal milieu, the nervous system is prepared and capable of responding to such interactions.

Depression is associated with the presence of biomarkers of inflammation such as elevated interleukin (IL)-6, tumor necrosis factor alpha, and the acute phase protein, C reactive protein (45). Similar elevated biomarkers of inflammation have been seen in anxiety states and are known to occur as a result of stress. The site at which these proinflammatory molecules is produced in depression is not known and it has yet to be determined whether the elevation is core to the pathophysiology or merely epiphenomenal. There is evidence from rodent studies to indicate that stress alters the gut barrier function, allowing lipopolysaccharide and other molecules to gain access to the bloodstream, stimulating TLR4 and other TLRs resulting in the production of inflammatory cytokines (46). If this does occur in depression, which has yet to be demonstrated, it would help explain the pro-inflammatory phenotype observed.

In the past, infectious diseases were thought to be the cause of many psychiatric disorders. Syphilis is a good example with central neurological deficits, including dementia, resulting from chronic infection. Lyme disease is a multisystem disease caused by infection with the *Borrelia burgdorferi* spirochete. The most common chronic symptoms reported include poor memory and concentration and a range of other neuropsychological deficits (47). Depressive states are also common, occurring in 26% to 66% of affected patients. Thus, it is long recognized that microbial pathogens can produce a depressive syndrome. How is such a syndrome induced and is it possible that commensal bacteria may have a reverse action and alleviate depressive symptoms? The evidence points to the fact that immune activation in the periphery can lead to central neurotransmitter changes. Pathogenic bacteria in doses that do not elicit sickness behavior can also bring about central changes. Lyte *et al.* (48) have shown that oral administration of the pathogen *Campylobacter jejuni*, in

subclinical doses, which were too low to elicit overt immune activation, resulted in anxiety-like behavior in mice. They also reported that areas of brainstem activation, most notably the nucleus tractus solitarius and lateral parabrachial nucleus, participate in neural information processing that lead to autonomic, neuroendocrine, and behavioral responses.

While an infectious etiology of mood disorders is not currently a major focus of research, elevated proinflammatory biomarkers are themselves associated with so-called sickness behavior, a term used to describe behavioral changes secondary to inflammation caused by infections, such as disturbances of mood, sleep, appetite, and fatigue (49). It is not clear whether peripherally produced inflammatory cytokines can directly affect the brain, but they have been shown to cause an increase in the permeability of the blood brain barrier (50). However, systemically injected inflammatory cytokines such as interferon- $\alpha$  are associated with the induction of depressive symptoms, which can be prevented by antidepressant therapy (51,52).

It has been hypothesized that the major classes of antidepressants work, in addition to their effects on central monoamines, by the generation of the potent immunoregulatory cytokine, IL-10, thereby suppressing inflammation and the central nervous system changes associated with depression (53). In this regard, it is interesting that the immunoregulatory effects of probiotic microorganisms are also thought to occur through the generation of T regulatory cell populations and the synthesis and secretion of IL-10 (39,54). Macpherson and Uhr (55) showed that feeding of a commensal bacteria to GF mice resulted in local dendritic cell uptake and alteration of phenotype to one that promoted Treg production and IL-10 synthesis. Ingestion of *Lactobacillus* GG has been suggested as therapeutic in management of several conditions and has been shown to upregulate IL-10 in the plasma of such patients (56). While IL-10 has potent anti-inflammatory properties, it is also thought to act directly as an antinociceptive agent, indicating that it has broad neuro-immune effects, but impact on behavior has not to date been reported. The intestinal microbial balance may alter the regulation of inflammatory responses and in so doing may be involved in the modulation of mood and behavior (57,58) (Figure 1).

### Microbiota and Hypothalamic-Pituitary-Adrenal Axis

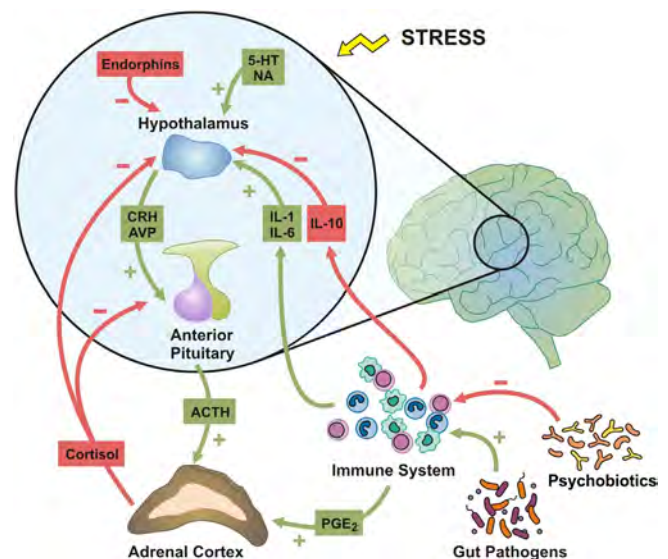
The use of GF animals has provided one of the most significant insights into the role of the microbiota in regulating the development of the hypothalamic-pituitary-adrenal (HPA) axis. Subsequent comparison with their conventionally colonized counterparts allows inferences to be drawn regarding the morphological and physiological parameters that may be under the influence of the developing microbiota. However, in the absence of the resident enteric microbiota, key members of the TLR family have low or absent expression profiles in the gut, thus compromising appropriate neuroendocrine responses to pathogens (59,60). For example, the TLR4 knockout mouse does not respond to gram negative bacteria with an activation of the HPA (61).

Pivotal studies by Sudo *et al.* (62) provide insight into the role of the intestinal microbiota in the development of the HPA axis. In GF mice, a mild restraint stress induces an exaggerated release of corticosterone and adrenocorticotrophic hormone compared with the specific pathogen free (SPF) control animals. The stress response in GF mice is partially reversed by colonization with fecal matter from SPF animals and fully reversed by monoassociation with *B. infantis* in a time-dependant manner (62). This

study clearly demonstrated that the microbial content of the gut is critical to the development of an appropriate stress response later in life and also that there is a narrow window in early life where colonization must occur to ensure normal development of the HPA axis (Table 1).

The question emerges whether the gut microbiota can have an influence over neural circuits and behavior associated with the stress response? Sudo *et al.* (62) reported a decrease in brain-derived neurotrophic factor (BDNF), a key neurotrophin involved in neuronal growth and survival, and expression of the *N*-methyl-D-aspartate receptor subunit 2A in the cortex and hippocampus of male GF animals compared with SPF control animals. On the other hand, Neufeld *et al.* (63) actually found an increase in hippocampal BDNF messenger RNA (mRNA) in female mice that was contrary to the protein decreases observed in the earlier study. We have recently also found decreases in hippocampal BDNF mRNA levels, as well as distinct changes in the serotonergic system in male but not female mice (64). This suggests that the regulation of microbiome-gut-brain axis may be sex dependent. Alterations in hippocampal *N*-methyl-D-aspartate and serotonin 1A receptor expression in GF animals has been shown in a number of studies (62). Both of these receptors are known to influence corticotropin-releasing hormone release from the hypothalamus and changes in expression may explain altered HPA function in such animals.

It is long known that stress and the HPA can influence the composition of the gut microbiome. However, the functional



**Figure 1.** Psychosocial stress is a dominant factor in the genesis of major depression. Stress results in activation of the hypothalamic-pituitary-adrenal axis by bringing about the release of corticotropin releasing hormone (CRH) and vasopressin (AVP) together with altered gut barrier function. The latter may result in the passage of lipopolysaccharide and other molecules into the bloodstream with development of a proinflammatory phenotype, characterized by high interleukin-1 (IL-1) and interleukin-6 (IL-6) levels. Prostaglandin  $E_2$  ( $PGE_2$ ) produced as a result of immune activation can directly stimulate the adrenal cortex. Conventional antidepressants act directly on monoamines and also suppress inflammatory cytokines. Psychobiotics elevate the anti-inflammatory cytokine interleukin 10 (IL-10), decrease proinflammatory cytokines, and suppress hypothalamic-pituitary-adrenal axis activity. They also act as a delivery vehicle for neuroactive molecules such as gamma-aminobutyric acid and improve gut barrier function. ACTH, adrenocorticotrophic hormone; 5-HT, serotonin; NA, noradrenaline.



**Table 1.** Psychobiotic Studies

	Findings
Preclinical	
Germ Free Studies	↓ behavioral but ↑ endocrine response to stress (62) Altered serotonergic development (63), BDNF, and glutamate expression (62) Partial reversal by <i>B. Infantis</i> (64) or fecal ingestion (62)
Maternal Separation Model of Depression	<i>B. Infantis</i> normalizes behavior (68)  Contradictory findings for psychobiotic effects on corticosterone (68–70)
Restraint Stress and Social Stress	Altered microbiota and ↑ proinflammatory cytokines (66,67)
Acute Stressors (e.g., Elevated Plus Maze)	<i>L. Rhamnosus</i> is anxiolytic and acts via the vagus nerve to produce changes in GABAA and GABAB expression (75)
Human Studies	
Irritable Bowel Syndrome	<i>B. Infantis</i> effective and alters plasma pro-inflammatory to anti-inflammatory cytokine ratio (77)
Chronic Fatigue Syndrome	↓ anxiety in those given <i>L. casei</i> relative to placebo (80)
Healthy Volunteer Studies	<i>L. Helveticus</i> together with <i>B. longum</i> ↓ psychological distress relative to placebo and ↓ urinary free cortisol output (71)

BDNF, brain-derived neurotrophic factor; GABAA, gamma-aminobutyric acid type A; GABAB, gamma-aminobutyric acid type B.

consequences of such changes are now only being understood. Maternal separation, an early life stressor that can result in long-term HPA changes, also has long-term effects on the microbiome (14,65). Analysis of the 16S ribosomal RNA diversity in adult rats exposed to maternal separation for 3 hours per day from postnatal days 2 to 12 revealed a significantly altered fecal microbiome when compared with the nonseparated control animals (36). A study using bacterial tag encoded FLX amplicon pyrosequencing demonstrated that the community structure of microbiota from mice exposed to a prolonged restraint stressor was significantly different from the community structure found in nonstressed control mice (66). More recently using the same approach, repeated social stress has been shown to decrease the relative abundance in bacteria of the genus *Bacteroides*, while increasing the relative abundance of bacteria in the genus *Clostridium* in the cecum (67). The stressor also increased circulating levels of IL-6 and monocyte chemotactic protein-1 (MCP-1), which were significantly correlated with stressor-induced changes to three bacterial genera (i.e., *Coprococcus*, *Pseudobutyri-ivibrio*, and *Dorea*).

Demonstrating changes in glucocorticoid levels in either rodents or man based on single serum samples is notoriously unreliable. In a maternal separation model, Desbonnet *et al.* (68) found behavioral changes with *B. infantis* treatment but no reduction in corticosterone, while using a similar model, Gareau *et al.* (69) found that feeding a *Lactobacillus* reduced corticosterone levels and McKernan *et al.* (70) found that *B. infantis* administration reduced corticosterone levels, though the reduction did not reach statistical significance.

In a recent clinical study, healthy volunteers were given *L. helveticus* R0052 and *B. longum* R0175 in combination or placebo in a double-blind, randomized parallel group study for 30 days (71). Twenty-four hour urinary free cortisol output was

reduced with probiotic treatment. However, no in-depth analysis in man of HPA activity in response to a course of any putative probiotic has been undertaken either in healthy subjects or patient populations. Nonetheless, based on the currently available data, Dinan and Cryan (72) concluded that developmental studies and those involving stress-related disorders should include the gut microbiota as an important regulator of the HPA and failure to do so can result in the introduction of a significant confounding variable.

## Psychobiotics and Neurotransmission

Over the past 25 years, well-tolerated antidepressants have emerged that largely target 5-HT and/or norepinephrine (NE). However, not all patients respond to antidepressants and some patients are averse to pharmacologic interventions. From a biological perspective, it is known that depressed patients frequently have HPA alterations, such as elevated cortisol levels in plasma, elevated corticotropin-releasing hormone levels in the cerebrospinal fluid, and a failure to suppress cortisol in response to dexamethasone challenge (73). Antidepressant treatment is accompanied by reversal of these abnormalities. As mentioned above, the hyper-response of the HPA in GF mice is reversed by monoassociation with a single organism, *B. infantis*, which is a predominant bacterium in the infant gut and a commonly used probiotic organism. Furthermore, in GF animals, the levels of NE and 5-HT in the cortex and hippocampus are significantly reduced (63). Thus, preclinical data clearly show that commensal bacteria have the capability of altering not only the HPA axis but key neurotransmitters thought to be of relevance in the etiology of depression.

Desbonnet *et al.* (68) assessed the potential benefits of the probiotic *B. infantis* in the rat maternal separation model of depression, a paradigm that has proven to be of value in the study of antidepressant effects. Maternally separated adult rat offspring were chronically treated with *B. infantis* or the selective serotonin reuptake inhibitor citalopram and subjected to the forced swim test to assess motivational state. Cytokine concentrations in stimulated whole blood samples, monoamine levels in the brain, and central and peripheral HPA measures were also analyzed. Maternal separation reduced swim behavior and increased immobility in the forced swim test, decreased NE content in the brain, and enhanced proinflammatory peripheral IL-6 release and amygdala corticotropin-releasing factor mRNA levels. Probiotic treatment resulted in reversal of behavioral deficits, normalization of immune response, and restoration of basal NE concentrations in the brainstem. These findings point to an influential role for *Bifidobacterium* in neural function and suggest that probiotics may have broader therapeutic applications than previously considered.

An in-depth analysis of the microbiota in depression and other stress-related disorders needs to be undertaken. The preclinical data strongly support the view that an aberrant microbiota can alter behavior, immunity, and endocrinology. Studies indicate that such an aberrant microbiota can be replaced with a healthy flora by fecal transplantation, as shown in patients with treatment refractory *C. difficile* infection (74).

Bravo *et al.* (75) examined the impact of *L. rhamnosus* on behavior and central GABA receptors in mice. Animals fed *L. rhamnosus* demonstrated reduced anxiety on a variety of behavioral measures and altered central expression of both GABA type A and GABA type B receptors. To determine the mechanism of action, animals underwent vagotomy or sham surgery and were

treated either with *L. rhamnosus* or inactive broth. Vagotomy prevented the emergence of an anxiolytic effect from the probiotic and prevented changes in GABA receptor expression. The study provides compelling evidence to indicate that the vagus mediates the behavioral and neurochemical effects of *L. rhamnosus*.

## Clinical Studies

Irritable bowel syndrome is a disorder of the brain-gut axis and is associated with a high degree of comorbid depression and anxiety (76). Several well-designed studies of probiotics have been conducted in this disorder (77,78). O'Mahony *et al.* (77) carried out a parallel group, placebo-controlled study comparing *B. infantis* and *L. salivarius*. The latter had little impact on symptoms, while *B. infantis* resulted in significant improvement. This therapeutic benefit occurred within the context of a reduction in proinflammatory cytokines.

In a recent double-blind, placebo-controlled, randomized parallel group study, volunteers received either the probiotic combination *L. helveticus* R0052 and *B. longum* or placebo for 30 days and were assessed by the Hopkins Symptom Checklist, the Hospital Anxiety and Depression Scale, the Perceived Stress Scale, and the Coping Checklist (71). Daily administration of probiotic combination significantly reduced psychological distress in volunteers, as measured by the Hopkins Symptom Checklist scale, the Hospital Anxiety and Depression Scale, and by the Coping Checklist. Furthermore, urinary free cortisol levels were significantly reduced by the probiotics, providing a potential mechanism for the improvement in psychological symptoms observed.

Another study by Benton *et al.* (79) found that the consumption of a probiotic-containing yogurt improved mood. One hundred thirty-two physically healthy subjects with a mean age 61.8 years volunteered in response to local media coverage. One hundred and twenty-four completed the trial. For a 3-week period, either a probiotic-containing milk drink or a placebo were consumed daily. Mood and cognition were measured at baseline and after 10 and 20 days of consumption. When the third with the lowest baseline mood were considered, they selectively responded by reporting themselves as happy rather than depressed after taking the probiotic.

In a study of patients with chronic fatigue syndrome, subjects were treated three times daily with *Lactobacillus casei* strain Shirota or a placebo with identical taste and appearance (80). Overall, there was a significant improvement in anxiety among those taking the active *Lactobacillus casei* strain Shirota compared with the placebo, providing further support for the view that a probiotic may have psychotropic effects.

## Whither Psychobiotics?

There are sufficient preclinical data to support the view that clinical studies with probiotics in depression are worth conducting. It is equally clear that not all probiotics are the same and most do not have psychobiotic potential. Numerous putative probiotics studied in our laboratory were found to have no demonstrable impact on behavior. To detect psychobiotics, we would favor probiotic strains that preclinically have shown behavioral effects, are delivery vehicles for neuroactive compounds, and have a capacity to decrease proinflammatory cytokines and reduce HPA activity. Such a profile is far broader

than that of a simple anti-inflammatory molecule. Clinical trials will need to be adequately powered with appropriate placebo control. A careful examination of data from the irritable bowel syndrome studies so far conducted may give clues as to the subtype of depression most likely to respond to probiotics. There is no doubt that many patients would value the emergence of nonconventional antidepressants in the form of psychobiotics.

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*TGD has until recently been on the Board of Alimentary Health. Each of the authors has spoken at meetings sponsored by food and pharmaceutical companies.*

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