Lallemand Health Solutions provides a selection of targeted probiotic strains, with specifically designed formulations that can help moderate psychological and pysiological responses to occasional stress.

Available in:
- Powders and orodispersible powders
- Capsules
- Chewable tablets
- Sticks or sachets
- Powders and orodispersible powders
- Capsules
- Chewable tablets
- Powders and orodispersible powders
- Capsules
- Chewable tablets

REFERENCES


The whole concept of what is now known as the Microbiota-Gut-Brain (MGB) axis [Rhee 2009] finds its roots in the late 19th century, early 20th. It is really with its advanced gene sequencing technologies and meta-genomics that the key role played by the digestive microbiota in our main physiological functions (e.g. digestion, immunity, endocrine and nervous systems) has come to light and regularly makes it into the mainstream media.

Surprising at first, this takes all its sense if we look at the way these two major organs develop at the same time in the embryo, creating an intimate relationship. Scientists have now cumulated evidence about the cross-talk between the brain and our gut. Furthermore, they have showed that the digestive microbiota plays a pivotal role in this bi-directional dialogue between our nervous and digestive systems.

What’s bugging you?

We have all experienced the incredible link between our brain and our gut. Just when we need to be at our best (i.e. an important event, an exam, a first day in a new job, a big meeting, etc.), our gut seems to have a mind of its own. Who is to blame? More and more scientific evidence points at the Brain-Gut axis, also known as our “second brain”, referenced amongst scientists as a bi-directional dialogue referenced amongst scientists at the Brain-Gut axis, also known as our “second brain”, referenced amongst scientists as a bi-directional dialogue of research since 2006; documenting the specific benefits of three of its flagship probiotics (Probio’Stick®, Lacidofil®, Bifidobacterium bifidum Rosell®-71) with the publication of 16 mechanistic studies and 3 clinical studies. Probio’Stick®, a dedicated probiotic formula and the first of its kind, was clinically proven in 2010 to moderate general feelings of anxiety and promote a healthy mood balance in those experiencing mild to moderate stress resulting from life events.

How far can probiotics go?

Probiotics have spurred many hopes and promises as a result of their interactions with the Brain-Gut axis. As a pioneer in the probiotic industry since 1934, Lallemand Health Solutions has committed to contribute strongly in this new field of research since 2006; documenting the specific benefits of three of its flagship probiotics (Probio’Stick®, Lacidofil®, Bifidobacterium bifidum Rosell®-71) with the publication of 16 mechanistic studies and 3 clinical studies. Probio’Stick®, a dedicated probiotic formula and the first of its kind, was clinically proven in 2010 to moderate general feelings of anxiety and promote a healthy mood balance in those experiencing mild to moderate stress resulting from life events. New research is now shedding some promising light on the role of the microbiota in more severe conditions and even major psychiatric disorders such as chronic fatigue, depression, autism, schizophrenia, thus paving the way for new management strategies for the future.

Early 2000s: the new pioneers

In the years that followed, further in vivo studies using challenge models with infectious microorganisms (see: “Animal Stress Model-Quick Reference Guide” p. 9) demonstrated an impact of digestive microorganisms on behavior, the activation of immune-neural mechanisms. It is only in 1998 that Lyte demonstrated in mice a direct activation of neural pathways by gut microorganisms with consequences on behavior, in particular anxiety, in the absence of an overt immunological response. In 2004, Sudo demonstrated in a fundamental study that postnatal microbial colonization programs the hypothalamic-pituitary-adrenal system (HPA) for stress response in germ-free mice.

In 2006, the first in vivo study testing a probiotic formulation (Lacidofil®) in a model of chronic psychological stress was conducted. Using the water avoidance stress model, Zareie et al. showed that the probiotic supplement was effective to prevent stress-induced intestinal abnormalities such as bacterial adhesion and translocation. The following year, using a model of maternal separation on adult rat behavior [Gareau 2007], the results on bacterial adhesion and translocation were confirmed.

In addition, they also showed an improvement of gut permeability with Lacidofil®. Remarkably, the probiotic was able to normalize the level of the stress hormone in the body (circulating corticosterone). Those beneficial effects carried on in older rats treated with the probiotic as neonates. The authors concluded that the probiotic “improved gut dysfunction induced by maternal separation at least in part by normalization of HPA axis activity”.

That same year, Eutamene tested three different probiotic strains (L. paracasei, B. lactis, L. johnsonii) again in a maternal separation model of stress and showed that only L. paracasei was able to significantly improve stress-induced visceral pain and restore normal gut permeability, demonstrating a strain specific effect.
In 2007, a clinical study explored, for the first time, the impact of probiotic intake on mood and cognition ([Benton 2007]). The motivation behind the study was that frequency of constipation had been found to correlate with a poor mood. The investigators recruited 124 healthy people, average age of 61.8 years, and randomized them into a placebo group or a probiotic milk drink with L. casei. The probiotic did not generally change the mood and the intervention did not influence the incidence of constipation, which was already low. However, in a subgroup of subjects whose mood was initially poor, there seemed to be some improvement with the probiotic.

In 2008, Desbonnet measured for the first time a direct brain level effect of a long-term probiotic intake, in a forced swim model of stress in rats. Even though swimming behavior was not different in the probiotic and placebo groups, the concentration of 5-HIAA (e.g. serotonin metabolite) was reduced in the frontal cortex while DOPAC (dopamine metabolite) was decreased in the amygdaloid cortex of rats treated with the probiotic. That year, Prof. Desor, an expert in cognitive science from Pointcaré University in France, demonstrated that in a situation of acute stress (conditioned defensive burying test), rats treated with Probio'Stick® exhibited similar behavior to valium-treated rats. This pioneering work was presented to an audience of researchers in both animal and human sciences at the first International Scientific Exchange dedicated to microbiota and the Brain-Gut axis, organized by Lallemand Health Solutions in November 2008 in Quebec City and published in November 2010 ([Messaoudi 2010]).


text

An intimate relationship

THE GUT: OUR SECOND BRAIN

- Brain and gut communicate through a vast network of 500 million neurons innervating the gut, the Enteric Nervous System (ENS).
- This vast web of connections monitors the entire digestive tract from the esophagus to the anus.
- ENS is so extensive that it can operate as an independent entity without input from our central nervous system.

Notwithstanding, they communicate regularly.

CHRONIC STRESS: A WORLDWIDE PANDEMIC

Associated to modern lifestyle, chronic stress is often described as a worldwide pandemic. Take the US as an example. Year after year, the Stress in America™ survey indicates increasing levels of stress in adults.

In 2015:
- 1/3 reported increased stress levels over the past year
- 24% reported extreme levels of stress
- 78% reported experiencing at least one symptom of stress

Knowing that chronic stress is increasing health risks for problems such as anxiety, depression, cardiovascular diseases, and obesity, stress management is key!

In this context, natural solutions such as probiotics could play a major role…
2010s: “of mice and men”... learning from animal models

The science of the MGB relationships is fascinating and at the crossroad of many disciplines amongst others neurology, cognitive science, gastroenterology, microbiology, immunology, etc. Research has taken many different paths, each bringing a new piece to the puzzle.

In-depth investigation of mechanisms of action continued with numerous animal studies focusing specifically on the MGB axis; all characterized by the use of the latest available technologies to measure an increasing number of physiological, hormonal, immunological or neural parameters, in an attempt to better capture the complete inner workings between each key players (see: MBG Axis, what we know on how it works).

**In 2010, Desbonnet replicated a maternal separation study but with a different bacteria strain and measuring more parameters. It was shown that norepinephrine was restored to levels in the brainstem associated with a reversal of behavioral deficits. Furthermore, the immune response was normalized with the probiotic.**

**That same year, Gareau et al. conducted a new study with Lacidophil® confirming the involvement of the HPA axis to mediate probiotic benefits in stress situations. The team went one step further in 2011 by looking at the effect of the microbiota on cognitive functions. They used an infection model of stress in mice and germ-free mice (with C. rodentium). The team demonstrated that the microbiota plays a role in memory function and that the administration of Lacidophil® prior to and during the experimental infection could prevent the stress-induced memory dysfunction.**

**From 2009 to 2012, the team of Prof. Rousseau, from University of Montreal (Canada), conducted several studies using a rat model of depression: post-myocardial infarction (MI) depression. This model of depression is accompanied by a production of pro-inflammatory cytokines, the “programmed death” of brain cells (apoptosis) in the limbic system (i.e. area of the brain implicated in emotions such as depression). It is also associated to an increased intestinal permeability and depression-like behavior. In a first study in 2009, Girard et al. showed that the prophylactic administration of Probiostick® prior to MI was able to reduce apoptosis in the rat limbic system. This innovative study showed a direct link between microbiota administration and the brain. The authors tested this hypothesis in a second study (Arseneault-Bréard et al., 2012).**

**Not only did Probiostick® reduce pro-inflammatory cytokines and restore gut barrier integrity but several behavioral tests showed that the probiotic treatment was able to significantly reduce the signs of depression in all of them, restoring baseline levels. The authors concluded that the probiotic administration can prevent behavioral despair, abnormal social behavior and blighted processing of emotional memory induced by post MI depression.**

**In the same period, Collins et al. at McMaster University (Canada) managed to change the behavior of mice by exchanging their microbiota! They studied two specific strains of mice that are known to exhibit very different behaviors: BALB/c mice are more anxious, whereas NIH Swiss mice are more friendly and exploratory. Using germ-free mice from both strains and implanting the microbiota from the other strain, they observed that exploratory NIH Swiss mice that received the BALB/c microbiota were much more resistant to anxiety, whereas the normally anxious BALB/c mice were very exploratory. Brain changes were measured and indeed corresponded to increased anxiety in the NIH Swiss mice whereas the BALB/c mice exhibited decreased anxiety. In 2013, Ohland demonstrated with wild-type mice (“normal” mice) and IL-10 deficient mice (mice prone to infection) that anxiety-like behavior and memory were negatively affected by Western-style diet. Results depended on inflammatory state. This change could be prevented by supplementation with L helveticus Rosell®-52 present in both Probiostick® and Lacidophil® in a different ratio.**
In 2015, other teams used various stress models and probiotic strains showing positive results in behavior and cognitive functions. For instance, Llang et al. used L. helveticus NS8 in adult pathogen-free rats in a model of chronic restraint stress, showing consistent positive results with the probiotic. The induced stress was followed by behavioral testing (sucrose preference test, elevated-plus maze test, open-field test, object-recognition test, and object-placement test), and the measure of a number of neurotransmitters and hormones associated to stress. What is the outcome? Li et al. selected a L. plantarum strain in a germ-free mouse model showing potential to reduce anxiety-like behavior with the live bacteria vs heat-killed bacteria and increase of dopamine and serotonin levels in the striatum. Savignac showed that a B. longum strain had a positive impact on cognition in a specific type of mice displaying high levels of anxiety, contrary to a B. breve strain that did not exhibit such an effect.

In 2016, another brick in the wall with two avant-garde publications from Cowan, Callaghan and Richardson from the School of Psychology at University of New South Wales, Sydney, Australia. Cowan conducted five experiments of maternal separation in rats to demonstrate that Lacidofil® could restore normal developmental trajectories of emotion-related behaviors in infant rats exposed to early-life stress. Then, they went one step further with 13 experiments over two generations of male rats to assess whether generational effects of stress on learning is evident in infant offspring, and whether probiotics can function as an active treatment or an effective prevention treatment to reverse the effects of paternal stress on F1-generation offspring. The team demonstrated for the first time longer-lasting aver-sive associations and greater relapse in the offspring (F1 generation) of rats exposed to maternal separation (FO generation), and the effect of paternal stress models and probiotic strains on the Brain-Gut axis.

Research boom

Between 2004 and October 2016, over 1,000 scientific publications and reviews have been published on the Brain-Gut axis, an exponential rate.

Meanwhile in France, an INRA (Institut National de Recherche Agronomique) team led by Dr. Ait-Belgnaoui, used a mice model of water-avoidance stress to further investigate the modes of action of a probiotic supplement (ProbioStick®). In 2014, they published a noteworthy communiqué showing that pre-treatment with this probiotic formula modulates neural network coordinating synaptic plasticity. Two results were found: significant reduction of neuronal activation in the same three regions of the brain activated by stress (hypothalamic paraventricular nucleus, amygdaloid nucleus and hippocampus dentate gyrus), and prevention of stress-induced reduction of neurogenesis to therefore exert a positive effect on dendritite development.

In 2015, other studies tested the effect specificity of Probio’Stick® (Institut National de Recherche Agronomique) team led by Dr. Ait-Belgnaoui (Institut National de Recherche Agronomique) team led by Dr. Ait-Belgnaoui, used a mice model of water-avoidance stress to further investigate the modes of action of a probiotic supplement (ProbioStick®). In 2014, they published a noteworthy communiqué showing that pre-treatment with this probiotic formula modulates neural network coordinating synaptic plasticity. Two results were found: significant reduction of neuronal activation in the same three regions of the brain activated by stress (hypothalamic paraventricular nucleus, amygdaloid nucleus and hippocampus dentate gyrus), and prevention of stress-induced reduction of neurogenesis to therefore exert a positive effect on dendritite development.

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**Animal Stress Models**

A Quick Reference Guide

Scientists have found various ways to simulate stress in lab animals. Below is a quick reference guide to animal models used in the studies presented.

<table>
<thead>
<tr>
<th>Model</th>
<th>Principle</th>
<th>What Does It Tell Us?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conditioned defensive burying</td>
<td>Based on the natural tendency of rats to bury a source of stress. An electric probe is placed in the cage. Each time the animal touches the probe, its behavior is recorded: duration of probe burying, movements towards and away from the probe.</td>
<td>To assess the level of stress and in particular anxiety.</td>
</tr>
<tr>
<td>Forced swimming test</td>
<td>Rats are placed in a transparent cylinder filled with water with no escape route. The animal will swim and try to escape, and after a while it will stop trying and keep afloat. This immobility response is linked to depressive behavior and immobility time is translated into depressive symptoms.</td>
<td>It is a common test to assess efficacy of anti-depressants.</td>
</tr>
<tr>
<td>Passive avoidance test</td>
<td>Learning and memory test. The animal is placed in a chamber partitioned into two sections. As it moves into the second section, a mild shock is delivered through the floor. The number of trials needed to learn the test is recorded.</td>
<td>To assess the effect of a treatment on learning and memory behavior (decreased with depressive behavior).</td>
</tr>
<tr>
<td>Post-myocardial infarction depression</td>
<td>Myocardial infarction artificially induced in rats is followed by apoptosis in the limbic system of the brain.</td>
<td>Induces depression-like behavior.</td>
</tr>
<tr>
<td>Social interactions</td>
<td>Two animals are placed together in a cage for a certain time and the duration and number of social interactions are recorded.</td>
<td>Used to assess depressive behavior (less social interactions).</td>
</tr>
<tr>
<td>Water avoidance stress</td>
<td>The animal is placed on a platform surrounded by water to induce psychological stress (anxiety). A well-characterized psychological stress model with elevations of ACTH and corticosterone (involvement of the HPA axis).</td>
<td></td>
</tr>
<tr>
<td>Challenge model</td>
<td>Injection with a pathogen (negative microorganisms e.g. C. rodentium, C. jejuni, T. muris) or with a chemical agent triggering a massive gut inflammation (DSS colitis, TNBS): use of antibiotics (broad or selective elimination of the flora)</td>
<td>Altered behavior: increased anxiety.</td>
</tr>
</tbody>
</table>
In order to evaluate levels of stress and psychological symptoms in healthy people, several tools have been applied, including biomarkers and validated psychological scales typically used for the evaluation of anxiolytic drugs.

**Biomarkers**
- **Cortisol**, often known as the stress hormone, can be assessed in the urine and in the blood by measuring the accumulation of urinary free cortisol over a 24-hour period or at a given time in the blood or saliva. It shows activation of the HPA axis (see “When Stress Undermines Our Natural Defenses” p. 5) and is used to backup self-assessments of stress levels.
- **Adrenalin**, also known as epinephrine, is a hormone used by the Autonomous Nervous System (ANS) to mobilize energy resources in case of danger or stress; it creates increasing heart rate, arterial pressure, bronchi and pupil dilatation. Just as its precursor norepinephrine (also known as norepinephrine), it can be measured in blood or urine.

**Validated Psychological Self-Assessment Tests**
- **Hopkins Symptom Checklist-90 (HSCL-90)**: 90-item questionnaire to assess nine primary symptoms: somatization, obsessive-compulsive, interpersonal sensitivity, depression, anxiety, anger-hostility, phobic anxiety, paranoid ideation and psychoticism. It gives a global severity index used to assess overall psychological distress.
- **Hospital Anxiety and Depression Scale, or HADS**: classical 14-item test to assess anxiety and depression.
- **Coping Checklist (CCL)**: 14-item questionnaire assessing the degree to which recent life situations are perceived as stressful.
- **Perceived Stress Scale (PSS)**: 14-item questionnaire assessing the degree to which recent life situations are perceived as stressful.
- **Beck Depression Inventory**: self-report inventory of 21 multiple-choice questions, one of the most widely used psychometric tests for measuring the severity of depression.
- **Beck Anxiety Inventory**: self-report inventory of 21 multiple-choice questions used for measuring the severity of anxiety in children and adults (numbness and tingling, getting not due to heat, and fear of wind-case scenario).
- **Depression Anxiety Stress Scales (DASS)**: self-report of 42 items to be completed within five to ten minutes, each item reflecting a negative emotional symptom.
- **The Leiden Index of Depression Sensitivity-Revised (LEIDS-R)**: self-report measure of 34 items to assess cognitive reactivity. Before answering, participants are asked to take a few minutes to imagine how they would feel and think it they were to experience a sad mood (“Not a good day, but not truly down or depressed”). Then they indicate to which extent each of the 34 statements applies to them. An example of statement on hopelessness/suicidality: “When I feel down, I more often feel hopeless about everything”.

A growing wave of striking clinical studies

So many convincing results in animal models could only give way to a rising tide of striking clinical studies. It is in 2008 that for the first time in human history, a specific probiotic formula, Probio’S tick®, was demonstrated to improve gastro-intestinal symptoms related to stress in healthy people. This double-blind, placebo-controlled, randomized clinical study was conducted on 75 healthy volunteers subject to chronic stress. The severity of stress-induced symptoms was evaluated by self-assessment, using a 62-item questionnaire, and scored according to a visual analogue scale (VAS). The subjects received over a 3-week period either Probio’S tick® or placebo daily. At the end of this period, it was found that two stress-induced gastrointestinal symptoms, nausea/vomiting and abdominal pain, were significantly reduced as compared to placebo. Bloating/flatusence also tended to decrease. One step closer to demonstrate the beneficial role of a specific probiotic formula on the Brain-Gut axis in humans...

In 2009, two pilot studies focused on chronic fatigue, which is a severe and complicated disorder that cannot be explained by an underlying medical condition. With 59 participants randomized to placebo or L. casei, Rao found an important rise in both lactobacilli and bifidobacteria in the probiotic group which was associated with a significant decrease in anxiety symptoms, as assessed by questionnaire.

In an open pilot study, Sullivan followed the fatigue, health and physical activity in 15 participants taking a 3-strain probiotic yogurt for four weeks. Neurocognitive functions (e.g. short-term memory and capacity to concentrate) assessed by VAS were improved during the study period while there were no significant changes in fatigue with physical activity scores, and no major changes in the gastrointestinal micro-flora. Yamamura, in a prospective randomized cross-over study with fermented milk, followed the sleep and health perception of 29 healthy elderly. The actigraph measured an improvement in sleep efficiency confirming with the feedback from SF-36 questionnaire.

2010 was a pivotal year for LHS with a second pioneering study on Probio’S tick® preparation. For the first time it was clinically proven that a probiotic could help moderate general feelings of anxiety and promote a healthy mood balance in those experiencing mild to moderate stress resulting from life events (Messaoudi, 2010). In this randomized double-blind placebo-controlled study, psychological signs of stress were evaluated using a range of validated psychological assessment scales for anxiety, depression, stress and coping strategies that are normally used to evaluate anxiolytic drugs. In addition, a biomarker for stress was assessed: cortisol. Daily intake of Probio’S tick® for a period of one month significantly improved general signs of anxiety and depression and subject’s ability to cope with the stress of the events of everyday life. Those results were correlated by a decrease of cortisol levels in the urine for the probiotic group.

In 2011, a secondary analysis was conducted on a subgroup from that first study, subjects selected for their lower cortisol levels (less stressed subjects). Results in this subpopulation were also positive, and the authors concluded that the improvement in symptoms among subjects with low to mild stress levels suggests the value of prophylactic intake of Probio’S tick® in terms of digestive comfort and general well-being.
In 2013, Tillisch used for the first time functional magnetic resonance imagery in 36 healthy women. The test consisted of activities alternating between emotional and resting brain activity. They concluded that a 4-week intake of fermented milk probiotic products affected activity of brain regions that control central processing of emotion and sensation.

Healthy adults with non-pathologic levels of stress remain a key target for many studies. Obviously, the stress models used for rodents cannot be applied to people. Hence, scientists have validated university examination as a model of psychological stress in healthy adults. It is a relatively easy way to access a large population of healthy individuals submitted to a similar psychological stress at the same time.

A randomized clinical trial published in 2015 was performed in the US at University of Florida on healthy students for six weeks around semester exam time. Primary outcome was to determine the effect of three different probiotic strains, on proportion of days with cold/flue due to this type of psychological stress, in order to evaluate the probiotic effect on natural defenses in healthy stressed subjects [Langkamp-Henken et al., 2015]. However, levels of self-reported stress, salivary cortisol and gastro-intestinal symptoms were also evaluated in the trial. Further statistical analysis of the study enabled evaluation of the effect of the probiotics on stress and stress-related symptoms. The results of this secondary analysis were published in June 2016 [Culpapper et al., 2016]. They indicated that the following with probiotic strain *Bifidobacterium bifidum Rosell®-71*, stressed-induced diarrhea symptoms were reduced and lack of sleep due to stress was diminished. Moreover during periods of lowest hours of sleep, participants reported lower stress levels when on *Bifidobacterium bifidum Rosell®-71* than on placebo.

In 2016, Kato-Kataoka used a similar model in healthy medical students for eight weeks with a fermented milk containing L. casei and saw a significant elevation of anxiety one day before the examination and changes in various biomarkers of stress. Unfortunately, they could not conclude to an overall benefit on psychological stress as levels of cortisol were different at baseline between the placebo and the probiotic milk. However, the fermented milk reduced the total number of days with physical symptoms such as common abdominal and cold symptoms.

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**The Microbiota-Brain-Gut Axis: What We Know on How It Works**

Our brain and the microbes that inhabit our intestinal tract communicate by the Brain-Gut-microbiome axis. The underlying mechanisms involve neural pathways but also immune and endocrine pathways.

**The stress response in mammals is mainly regulated and controlled by the Hypothalamus-Pituitary-Adrenal axis (HPA axis).** This dominant component of the neuroendocrine system controls stress response and regulates bodily processes such as digestion and immunity. One of the main biochemical hormonal mediators of this pathway is the glucocorticoid cortisol. External factors (i.e. a traffic jam, fear, hostility, work, exams, etc.) can cause a stress response. This stress response causes the release of cytokines from our enteric immune cells which can impact the microbial composition to meet the body’s needs. The intestine can also send a message to the brain through neurotransmitters and other neuroactive compounds such as serotonin which goes systemically through blood circulation up to the brain. 

Our brain and our gut communicate by means of an intestinal network comprising 100 to 200 million nerves. This is why the gut is also known as the second brain. The enteric nervous system allows a bi-directional communication through blood vessels (after passing through intestinal barriers) and nervous pathways through the vagus nerve. It is essential that our central nervous system and our enteric nervous system communicate from the brain for digestion (motility) but also satiety and abdominal pain. It has been recently hypothesized that signals from the brain can impact the microbial composition to meet the body’s needs. The intestine can also send a message to the brain through neurotransmitters and other neuroactive compounds such as serotonin which goes systemically through blood circulation up to the brain. The gut microbiota is a major factor in this communication as it metabolizes ingested food into tryptophan, gamma-aminobutyric acid (GABA), opioid-like compounds and other potential neuroactive bioactive compounds. Specialized intestinal endocrine cells, enterochromaffins, located in the gut produce large quantities of the neurotransmitter serotonin from tryptophan and histamine which may be responsible for some of the major effects on signaling to the brain. Some bacterial species are able to produce these neuroactive indolamines from tryptophan. Bacteria can also modulate the release of cytokines from our enteric immune cells which in turn through systemic actions can modulate our limbic system (i.e. the portion of the brain involved in emotion, learning and memory) via the vagus nerve. The interactive relationship between the immune cells and the microbiota has been extensively studied and is reasonably well-defined. Additionally, some of the microbiota can digest carbohydrates into Short Chain Fatty Acids (SCFAs, such as acetate and butyrate) which are then taken up by the intestinal epithelial cells. These metabolites may also have a role in enteric neuro-signaling. Everything that can cause a dysbiosis can have an impact on the Brain-Gut axis. This could occur as a result of changes in diet, taking antibiotics or other medications, or an infection. The dysbiosis means a change in the microbiota and potentially a loss of bacterial diversity which could disrupt the positive mechanisms and result in production of different neuroactive signals, less production of metabolites, and production of more inflammatory cytokines. All of these can send negative messages to the brain which can result with apoptosis (programmed cell death) and loss of neuroplasticity in the limbic regions of the brain associated with mood, behavior, learning and memory (i.e. the hypothalamus, hippocampus and the amygdala).

Certain probiotics, when administrated orally, have been shown to reduce inflammation and to reverse stress-induced apoptosis in the limbic system as well as restore the neuroplasticity and decrease anxiety in healthy adults.
In 2015, Steenbergen demonstrated that in healthy young adults an 8-strain probiotic supplement could lower the activation of negative thoughts that accompanies a sad mood. No biomarker of stress was used in this study to assess the level of stress, but interestingly the investigator used a self-reported questionnaire used to predict depression (LEIDS-r scale). Out of the six categories assessed, “rumination” showed a significant difference. Moreover, no differences were observed on the other two scales used in the study (Beck Depression Inventory and Beck Anxiety Inventory).

Other healthy but at risk populations have also been studied. Mohammadi et al. in 2015 focused their study on petrochemical workers, assessing mental health parameters including General Health Questionnaire (GHQ) and Depression Anxiety and Stress Scale (DASS). Scores in both questionnaires were improved after six weeks in the probiotic yogurt and probiotic capsule groups but not in the conventional yogurt group. No results were reported on blood analysis.

In an open label study, De Roos followed 29 patients suffering from at least four migraine attacks per month. Daily self-report questionnaires were used to capture frequency and intensity (10-point Likert scale) of migraine attacks, use of medication and gastrointestinal complaints. Two scales (Migraine Disability Assessment Scale (MIDAS), Henry Ford Hospital Headache Disability Inventory (HDI)) were used as a baseline and followed the 12-week intervention for a more complete assessment. Number of migraines and intensity decreased significantly over time. Improvement was seen with the MIDAS scale but not on HDI.

In 2016, Akkasheh et al. followed 40 patients with Major Depressive Disorders (MDD), and demonstrated significant but still minor improvement with the probiotic supplementation. Many studies have been registered and are on-going in specific populations with severe conditions such as autism, Alzheimer, post-traumatic stress disorders or ADHD.

From everyday stress to psychological disorders

Today, with the growing acceptance and resonance of the MGB axis concept worldwide, new studies have emerged in sick populations or people with psychological disorders. In 2014, a pilot study in 30 patients with laryngeal cancer and 20 healthy volunteers as control was conducted by Yang et al., to evaluate the effect of a C. butyricum strain on improving anxiety before surgery. The study brought some positive results to light.

In 2016, Akkasheh et al. followed 40 patients with Major Depressive Disorders (MDD), and demonstrated significant but still minor improvement with the probiotic supplementation. Many studies have been registered and are on-going in specific populations with severe conditions such as autism, Alzheimer, post-traumatic stress disorders or ADHD.

The medicine of tomorrow: towards psychobiotics?

In 2013, the team of John Cryan coined the term “Psychobiotics” to describe a new class of probiotics: “a live organism that, when ingested in adequate amounts, produces a health benefit in patients suffering from psychiatric illness”.

New and on-going studies indicate some potential applications for the years to come in certain areas where the microbiota seems to play a key role: depression, autism, schizophrenia, and Alzheimer to name a few. The following is a quick overview of what we can expect in the future for said severe conditions.

In 2015, the team of John Cryan coined the term “Psychobiotics” to describe a new class of probiotics: “a live organism that, when ingested in adequate amounts, produces a health benefit in patients suffering from psychiatric illness”.

Depression is a very common disorder, (3-10% prevalence have been reported), linked to diminished role functioning and quality of life, medical morbidity, and mortality.

According to the WHO, it is the fourth leading cause of disability worldwide. A link has often been drawn between depression and leaky gut syndrome, digestive dysbiosis/infection as well as systemic inflammation. Moreover, depression is accompanied by a change of the microbiota in animal models. This has been hypothetically extrapolated to humans in a review called “Autism Spectrum Disorders (ASDs)”.

Autism and Asperger’s syndrome are usually diagnosed in early childhood. These disorders are characterized by problems with communication and social behavior. In recent decades, the reported prevalence of ASDs has dramatically increased from 4.5 in 10,000 children in 1966 to 1 in 110 in 2006, and to 1 in 68 children in 2010 (CDC: Centers for Disease Control and Prevention). Parents’ awareness and expectations are extremely high for progress and alternatives in these areas. In recent years, increasing evidence about the implication of the microbiota in ASD has been brought forward. Significant modifications of the microbiota composition have been reported in a rodent model. Similar changes were described in humans, with most changes observed in Clostridia and Bacteroides species. Additionally, autistic children show more frequent GI symptoms. The microbiota could play a role in the development of social behavior and the etiology of ASD. Assumed hypothesis is that the altered microbiota could lead to imbalances in carbohydrates and amino acids’ metabolism in the gut, leading to altered metabolite levels in the blood. A manipulation of the microbiota could bring a hopeful alternative to many patients and parents. Furthermore, probiotic intervention studies with autistic children are on-going.

Alternatives to psychotropic drugs for Schizophrenia are in high demand. It is shown that germ-free mice tend to show a schizophrenia-type behavior. Schizophrenic patients exhibit increased gut permeability and translocation of gut bacteria, indicating potential implication of the Microbiota-Brain-Gut axis.

Other clinical areas under the radar include diseases in which patients have shown significant differences in microflora, compared to suggesting probiotics may be implicated in the control of neuro-inflammation, suggesting a potential role for Alzheimer.

Other research paves the way for new hypotheses on the potential curative role of probiotics in traumatic brain injuries.
BENTON 2007 124 Mean age 61.8 RCT, Double blinded, placebo-controlled Yes Healthy volunteers Psychological stress L. casei Shirota in yoghurt once daily 1 dairy 3 weeks Mood and memory Hopkins Symptom Checklist-90 (HSCL-90), Visual analogue scale Questionnaire of eating-associated behaviour No No

No general effects of taking the probiotics were found when daily mood ratings and cognition were considered. Only improvements to mood to slowly to consider those who were more depressed at baseline (P = 0.04).

KATO-KATOMA 2016 47 Mean age 23 RCT, Double blinded, placebo-controlled Yes Students in period of exams L. casei Shirota in fermented milk once daily 1 dairy 8 weeks Psychological stress response POMS (Profile of Mood States) Questionnaires of eating-associated behaviour

No changes in the HADS-anxiety, HSCL depression, SDS and SDS scores with in or between both groups over time. Sleep quality improved and stress and life satisfaction were significantly improved with the group that received probiotics and the placebo group (P < 0.05).

OSIP 2006 79 Mean age 38 RCT, Double blinded, placebo-controlled Yes Healthy volunteers Psychological stress B. longum Rosell®-107 and/or L. casei Shirota Rosell®-71 (Probio'stick®) once daily 2 supplement 3 weeks No No

The consumption of Probiostick resulted in a significant improvement in abdominal pain and nausea/vomiting. No significant changes to other symptoms.

SULLIVAN 2005 15 Mean age 45 Open pilot study No Chronic fatigue patients Psychological stress L. casei Shirota in milk 3 times daily 1 dairy 2 months Anxiety and depression Beck Depression Inventory, Beck Anxiety Inventory No No

29.1% of patients had a greater than 50% improvement in fatigue symptoms by VAS. No significant differences in score between pre-treatment and post-treatment.

MESSAOUDI 2011 55 Mean age 32 RCT, Double blinded, crossover design Yes Healthy elderly Psychological stress L. helveticus DSM 17938, L. acidophilus DSM 17938, and S. thermophilus DSM 17938 twice daily 3 dairy 1 month Follow-up Physical and mental health SF-12 Health Survey No No

Fatigue symptoms by VAS showed no significant difference between the groups. No significant differences in score were noted between pre-treatment and post-treatment.

TILLISCH 2011 36 Women mean age 36 RCT, Crossover design Yes Healthy volunteers Psychological stress milk with B. animalis subsp. Lactis, B. thermopilus, and L. lactis subsp. Lactis twice daily 4 dairy 4 weeks No No

An increase in median cortisol response to an emotional intervention to measure brain response to emotional faces attention task and eating brain activity.

YANG 2014 50 Mean age 40-47 RCT, Placebo-controlled Yes and No 30 patients with long-term psychological problems Psychological stress B. bifidum twice daily 1 supplement 2 weeks Follow-up Physical and mental health Hamilton Anxiety Scale, Hamilton Depression Scale, SF-12 Health Survey No No

A significant reduction in the rate of experiencing physical symptoms and days experiencing physical symptoms (P < 0.05) than the placebo group. Baseline values for serum cortisol, L-tryptophan, faecal serotonin were not significantly different between groups.

STEDINGER 2010 45 Mean age 22 Triple-blind, placebo-controlled, randomized Yes Healthy Psychological stress B. infantis W23, B. longum W35, L. acidophilus W37, L. casei W58, and L. rhamnosus W32 (Ecologic®) once daily 8 weeks Follow-up Physical and mental health SF-12 Health Survey, SF-36 Health Survey No No

The probiotic treatment, in comparison to the placebo, significantly overall cognitive reactivity to sad mood (p = 0.019), and in particular reduced rumination (p = 0.001) and aggressive thoughts (p = 0.032).

MARRA 2010 50 Mean age 25 RCT, Placebo-controlled Yes Psychological stress B. longum Rosell®-107, L. acidophilus Rosell®-117, L. casei W56, and L. lactis BB-12 (Protexin®) twice daily 6 weeks Follow-up Physical and mental health SF-12 Health Survey, SF-36 Health Survey No No

A significant increase in median cortisol response to an emotional intervention to measure brain response to emotional faces attention task and eating brain activity.

MOHAMMADI 2015 70 Mean age 20-50 RCT, Double blinded, placebo-controlled Yes Petrolchemic workers Psychological stress Yogurt with L. acidophilus LA-5 & B. longum BB-12 and/or L. casei, L. acidophilus, L. bulgaricus, L. brevis, B. longum, and B. bifidum (Probiolact®) once daily 8 weeks Follow-up Physical and mental health SF-12 Health Survey No No

A significant increase in median cortisol response to an emotional intervention to measure brain response to emotional faces attention task and eating brain activity.

DE ROOS 2011 39 Age range 20-60 RCT, Double blinded, placebo-controlled No Chronic fatigue patients Psychological stress probiotic L. casei Shirota Rosell®-71 twice daily 1 dairy 3 weeks Physical and mental health SF-12 Health Survey No No

No significant changes to other symptoms. No significant changes to other symptoms.

ANKASHI 2014 45 Age range 20-53 RCT, Double blinded, placebo-controlled No Major depressive disorder (NDD), Psychological stress L. casei, L. acidophilus, L. casei Shirota Rosell®-71 3 times daily 3 supplement 8 weeks Physical and mental health Beck Depression Inventory, Beck Anxiety Inventory No No

No significant changes in (PSQI >50), number of ruminative thoughts (PSQI >50), number of sleep disturbances (PSQI >50), total sleep time <6 hours, sleep latency >10 minutes, time awake after insomnia, or sleep efficiency <80% in both groups.

CULPEPPER 2016 58 Mean age 19.0 RCT, Double blinded, placebo-controlled Yes Students in period of exams Psychological stress L. casei Shirota Rosell®-71 or B. infantis Rosell®-71 once daily 1 supplement 6 weeks Physical and mental health SF-12 Health Survey, SF-36 Health Survey No No

No significant changes in (PSQI >50), number of ruminative thoughts (PSQI >50), number of sleep disturbances (PSQI >50), total sleep time <6 hours, sleep latency >10 minutes, time awake after insomnia, or sleep efficiency <80% in both groups.

KATO-MATSU 2011 48 Mean age 23 RCT, Double blinded, placebo-controlled Yes Students in period of exams Psychological stress L. casei Shirota Rosell®-71 once daily 1 dairy 3 weeks Psychological stress response VAS, POMS, Beck Depression Inventory No No

No significant changes in (PSQI >50), number of ruminative thoughts (PSQI >50), number of sleep disturbances (PSQI >50), total sleep time <6 hours, sleep latency >10 minutes, time awake after insomnia, or sleep efficiency <80% in both groups.
Lallemand Health Solutions provides a selection of targeted probiotic strains, with specifically designed formulations that can help moderate psychological and physiological responses to occasional stress.

Available in
- Powders and orodispersible powders
- Capsules
- Chewable tablets

REFERENCES


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