In animal studies, stress imposed upon rat pups via a maternal separation model resulted in behavioural alterations suggestive of increased anxiety and perturbations in gut microbiota. Other phenotypic changes exhibited in these animals included visceral hypersensitivity, elevated hypothalamic-pituitary-adrenal (HPA) axis function and increased systemic immune responses. Increasingly, evidence is in concordance with the view that psychological stress can increase gut permeability, allowing passage of bacteria and bacterial antigens through the epithelial barrier. This can then activate a mucosal immune response while alters pro-inflammatory cytokines and activates the HPA. In other studies, it was also shown that stress hormones promoted the growth of non-pathogenic and pathogenic *E. coli* via interactions with host catecholamines such as adrenaline and noradrenaline.

While anxiety or stress has an effect on the composition of gut microbiota, it must be recognised that the microbiota can also affect stress response and central functioning, evident from an exaggerated corticosterone production in germ-free (GF) mice after acute stress. Studies have also found that gut microbiota coordinates peripheral availability of tryptophan, which is crucial for serotonin synthesis in the central nervous system. Serotonin is a key signalling molecule in the brain-gut axis, regulating functions like emotion, cognition, stress, visceral perception and gastrointestinal motility and secretion. Colonisation of GF animals resulted in normalisation of plasma tryptophan concentrations while administration of probiotic *B. infantis* increased its concentration. In other studies, exposure of rats to *L. helveticus* and *L. rhamnosus* prevented stress-induced increase in bacterial adherence to gut epithelium and translocation of commensal bacteria, while *L. paracasei* significantly improved stress-induced visceral pain and restored normal gastrointestinal permeability.

Traditionally, the focus of IBS management was primarily on symptom management of each individual, with little light shed on the benefits of probiotics which played more of a complementary role due to its lack of evidence. With accumulating evidence that the composition of the gut microbiota can be modulated, it poses as a promising therapeutic target and presents the potential of probiotics being a candidate of benefit to IBS patients.

Quick Facts

The brain has a direct effect on the stomach. For example, the very thought of eating can release the stomach's juices before food gets there. This connection goes both ways. A troubled gut can send signals to the brain, just as a troubled brain can send signals to the gut. Therefore, one's gastrointestinal distress can be the cause or the product of anxiety, stress, or depression.

Ref: Harvard Health Publications:
Healthbeat. The gut-brain connection.

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Message from the Editor

18th Edition

Hippocrates once said that all diseases begin in the gut and we could not agree more. Today, we see a lot of health conditions that are invariably linked to gut dysbiosis, like mental disorders, gastrointestinal problems, and autoimmune abnormalities.

Science is discovering the gut as the "second brain" in our body as the gut microbiota plays a vital role in our physical and psychological health via the enteric nervous system. Most of us can relate to the experience of having butterflies in our stomach, or a visceral gut-wrenching feeling. It is no doubt that the gut and the brain are intimately connected.

We hope this issue will change the way you look at the gut as we now know that a healthy gut maintains wellness and proper gut health has important treatment implications.

Sending warm wishes to all our readers from the team of The Probiotics News. May the Lunar New Year bring peace, happiness and good health to you and your family.

God bless!

Melvin Wong
Editor-in-chief

Probiotics on the brain

By **Kristina Campbell**, M.Sc.[1] and **Andreu Prados**, B.Sc.[2*]

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Human gut microbes function like an organ within the gastrointestinal tract, and major functions include metabolic activities that result in salvaging energy and absorbable nutrients, effects on intestinal epithelia and on immune structure and function, and protection of the colonised host against invasion by pathogens[1]. Increasing evidence points to a role for the gut microbiota in the regulation of brain and behaviour through the bidirectional network of communication between the gastrointestinal tract and the brain via the microbiota, termed the microbiota-gut-brain axis[2].

Research over the past few years reveals that the gut microbiota is required for proper development of the hypothalamic-pituitary-adrenal (HPA) axis, optimal stress responsivity, and social cognition[3]. The development of a healthy and functional brain depends on key pre- and post-natal events that integrate inputs from the periphery, such as molecular signals from the gut. Indeed, the development of the brain during the early postnatal period occurs adjacently to the development of the gut microbiota and there is an interdependence of brain and microbiota development[2]. The biological intersection of neurodevelopment and the microbiome is illuminated by data showing the role of the gut microbiome in several neurogenerative processes including the formation of the blood-brain barrier, myelination, neurogenesis, and microglia maturation. However, the mechanisms underlying the ability of the gut microbiota to influence behaviour remain unknown[4].

Experimental studies in germ-free animals (GF; microbiota deficient from birth) reveal the importance of gut microbial communities in regulating brain function. GF mice exhibit abnormal response to stress, anxiety-like behaviours, as well as deficits in social interaction[5]. These behaviours are also linked with observable brain morphology differences. A recent study[6] showed that the amygdala and hippocampus are brain regions

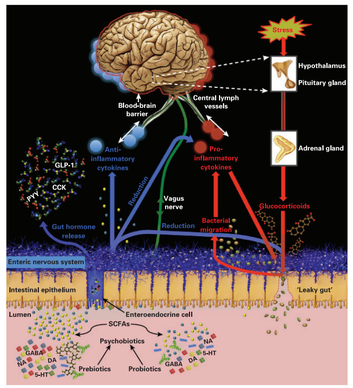
whose structural integrity is contingent on the presence of a gut microbiota. Another study[7] has demonstrated that upregulation of genes linked to myelination in GF mice, which can lead to a shortened life span, could be reversed by colonizing the mice with a conventional microbiota; this emphasizes the role of the microbiome for appropriate cortical myelination. In addition, bacteria can influence host production of proteins involved in promoting maturation and survival of developing neurons, such as BDNF (brain-derived neurotrophic factor). GF mice or those who have had their microbiota severely disrupted by antibiotics show decreases in the hippocampal expression of BDNF[8].

Physiological effects of the gut microbiota on the brain are not only mediated by microbes themselves, but also by biologically active small molecules that come from the gut bacterial metabolism and act as messengers throughout the body. Among these molecules, short-chain fatty acids (SCFAs) and gastrotransmissers produced by the human microbiota are of special interest. Some of these microbial metabolites are hypothesized to perform neuromediator and/or endocrine functions by modulating the expression of specific genes or by affecting the neural, immune, and endocrine gut-brain networks that are shaped in part by the gut microbiota[9]. Among others, important neurochemicals produced by gut bacteria include gamma-aminobutyric acid (GABA), norepinephrine, serotonin, dopamine and acetylcholine[10].

Dysregulation of the microbiota-gut-brain axis may contribute to the development of psychiatric and gastrointestinal diseases; this is supported by the association of intestinal dysbiosis with central nervous system disorders (e.g. anxiety-depressive behaviours), as well as functional gastrointestinal disorders (e.g. irritable bowel syndrome) that have mental health comorbidities.

Probiotics may be able to modify the bidirectional communication between the gut and the brain. Although psychobiotics were initially defined as a subset of probiotics which, when ingested in adequate amounts, produce a health benefit in patients suffering from psychiatric illness, a more up-to-date definition includes prebiotics and other means of influencing the microbiome beyond probiotics that may confer mental benefits[11]. A recent study[12] showed that treatment with *Bifidobacterium longum* 1714 strain for 4 weeks could reduce daily reported stress and improve memory in a sample of 22 healthy human volunteers. Results like these show the potential use of psychobiotics for the management of stress-related conditions.

Several studies have examined how mental benefits (e.g. in memory and cognition) can be modified by a high fibre diet and probiotics. Most of the data have been acquired using rodents and few human studies have assessed the effect of probiotic supplementation on mental health through modulation of brain-gut pathways. In a recent review[13], a high-fibre diet was hypothesized to prevent and/or treat brain disorders by elevating butyrate in the gut, since butyrate plays a role in altering gene expression in the brain and may prevent neurodegeneration. In addition, one study[14] showed that behavioural alterations in mouse offspring induced by a maternal high-fat diet can be restored via selective reintroduction of the commensal bacteria *Lactobacillus reuteri*.



Credit: Sarkar et al./Trends Neurosci 2016

It has been reported[15] that dysbiosis of the gut microbiome may be a contributory factor to the development of depressive-like behaviours, in a pathway that is mediated through the host's metabolism. A recent systematic review and meta-analysis of randomized controlled trials[16] found that probiotics were associated with a significant reduction in depression. Although further evidence from larger samples are needed to determine whether probiotics can significantly reduce the risk of depression, it opens a new door for preventing depression.

Regarding probiotic interventions for managing behaviours related to psychiatric disorders, a recent systematic review of 38 randomized controlled trials[17] in both animals and humans (25 in animals, 15 in humans, and 2 in humans and animals) concluded that probiotics could be effective in improving psychiatric disease-associated functions and memory abilities. Probiotics that showed efficacy in improving psychiatric disorder-related behaviours (anxiety, depression, mood, stress response) and memory abilities (including spatial and non-spatial memory) included Bifidobacterium (*B. longum, B. breve,* and *B. infantis*) and Lactobacillus (*L. helveticus, L. rhamnosus, L. plantarum,* and *L. casei*). Doses between 10^9 and 10^{10} colony-forming units (CFU) for durations of 2 weeks in animals and 4 weeks in humans showed sufficient effects. Although animal studies suggest possibilities, further human studies are worthwhile, especially for mental disorders that usually show gastrointestinal comorbidities. In addition to behavioural measurements such as psychological questionnaires or scales, more neuroimaging studies in humans are needed in order to study what area is altered in the brain that causes behavioural changes after the consumption of probiotics. On the other hand, a recent systematic review of 10 randomized controlled trials[18] in humans (including 6 trials that were also included in the Wang, et al. systematic review) provided limited support for the use of probiotics in reducing anxiety-depressive symptoms in humans. Although it seems that probiotic supplementation could lead to psychological benefits, substantial methodological limitations were found as the main problem in generalizing its findings. The researchers emphasized

that further follow-up intervention studies are needed in order to better understand the potential human mental health benefits of probiotic supplementation.

To sum up, gut bacteria are probably integral contributors to development and function of the nervous system and to the balance between mental health and disease. Taking into account the association of intestinal dysbiosis with central nervous system disorders and functional gastrointestinal disorders with mental health comorbidities, probiotics emerge as a novel therapeutic approach for individuals with these conditions. Further human studies are needed to elucidate which patients could benefit from probiotic supplementation for improving their mental function, as well as the dose, strains, and duration to develop evidence-based guidelines for the use of probiotics as a non-pharmacological option complementary to the recommended treatment for behaviour- and stress-related conditions. Further studies will also help unravel the mechanisms underlying such effects.

Gut and Psychology Syndrome (GAPS Syndrome or GAPS)™, 19-69

By
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We live in the world of unfolding epidemics. Autistic Spectrum Disorders, Attention Deficit Hyperactivity Disorder (ADHD), schizophrenia, dyslexia, dyspraxia, depression, obsessive-compulsive disorder, bipolar disorder and other neuro-psychological and psychiatric problems in children and adults are becoming increasingly common. In clinical practice these conditions overlap with each other. On examination, we find that these patients are also physically ill. Digestive problems, allergies, eczema, asthma, various food intolerances and immune system abnormalities are universally present. How are all these conditions related? One common factor is the state of their digestive system.

It is important to look at the health history of the parents, mother in particular. A modern mother very often has not been breast fed as a baby. It is known that bottle fed babies develop different gut flora to breast fed babies. A typical modern mum took antibiotics and oral contraception in adulthood, which damaged her gut flora even further. She grew up with processed and fast food, which feed pathogenic microbes in the gut. Abnormal gut flora is present in almost 100% of mothers of children with neurological or psychiatric conditions. Why are we talking about a mother's gut flora? Because in the first 20 or so days of life, a baby's virgin gut surface is populated by a mixture of microbes which come mainly from the mother at birth.

Gut flora performs vital functions for our survival:

1) Appropriate digestion and absorption of food: With poor digestion and absorption, nutritional deficiencies are common in children and adults with learning disabilities, psychiatric problems and allergies. Common deficiencies are magnesium, zinc, selenium, copper, calcium, manganese, sulphur, phosphorus, iron, potassium, vanadium, boron, vitamins B1, B2, B3, B6, B12, C, A, D, folic acid, pantothenic acid, omega-3, 6, 9 fatty acids, taurine, alpha-ketoglutaric acid, glutathione and many other amino-acids, which are vital nutrients for development and functioning of the brain, immune system and the rest of the body.

2) Active synthesis of nutrients: Majority of children and adults with neurological and psychiatric conditions look pale, being in various stages of anaemia. It is not surprising; blood production requires many nutrients: vitamins (B1, B2, B3, B6, B12, K, A, D, etc), minerals (Fe, Ca, Mg, Zn, Co, Se, boron, etc.), essential amino acids and fats. Healthy gut flora is a major source of these nutrients in the body. On top of that, pathogenic bacteria grow in their gut (Actinomyces spp., Mycobacterium spp., pathogenic strains of E.Coli, Corynebacterium spp, etc). They consume dietary iron, leaving the person deficient in iron. Supplementing iron makes these bacteria grow stronger and does not remedy anaemia. To treat anaemia, nutrients which a healthy gut flora supplies are required.

3) Immunological function: Gut flora plays a major role in immune function. At birth, a baby has an immature immune system. Inheriting a compromised gut flora leaves a baby immunocompromised and results in a continual cycle of infections and antibiotic courses, which damage the gut flora and immune system further. In the first two years of life the child also receives vaccinations. In many cases vaccines deepen the damage to the immune system and provide a source of chronic persistent viral infections and autoimmune problems. Damage inflicted upon the gut flora typically leads to imbalanced immunity, resulting in allergies, asthma and eczema. Considerable research has been published into the state of immunity in patients with learning disabilities and psychiatric issues, showing deep abnormalities in major cell groups and immunoglobulins. Autoantibodies most commonly found are myelin basic protein and neuron-axon filament protein, which specifically attack the brain and rest of the nervous system.

4) Housekeepers for digestive tract: They provide a natural barrier and nourishment for the gut lining. An estimated 60-70% of energy is derived from gut bacteria activity. A lack of beneficial bacteria allows propagation of pathogens, causing gut wall inflammation. Patients with learning disabilities, psychiatric disorders and allergies indeed present with digestive complaints and examination by gastroenterologists commonly reveals gut inflammation and often celiac disease. Two groups of pathogens commonly found on testing, are yeasts (including Candida species) and Clostridia family. They digest food and produce toxins, which are absorbed into the blood and cross the blood-brain barrier. The makeup of toxins can be individual, causing different neurological and psychological symptoms. Due to a scarcity of beneficial bacteria in the gut, the person's digestive system becomes a major source of toxicity instead of nourishing the body.

Some toxins which have received a considerable amount of research include:

1) Alcohol and its by-product, acetaldehyde
Among yeasts, the Candida species is particularly common to overgrow in the gut of patients with neuro-psychiatric conditions. Yeasts ferment dietary carbohydrates, producing alcohol and acetaldehyde, a condition first described by Japanese researchers in the 70s and 80s as "an auto-brewery syndrome". Constant exposure to alcohol and acetaldehyde can potentially cause:

- Reduced ability of liver in detoxification
- Pancreas degeneration with reduced ability to produce pancreatic enzymes
- Reduced ability of the stomach wall to produce stomach acid
- Damage to immune system
- Brain damage with poor self-control, impaired co-ordination, impaired speech development, aggression, mental retardation, loss of memory and stupor
- Direct muscle and nerve damage, altering senses and muscle function
- Deficiencies of vitamins, minerals and amino acids (commonly vitamin A, Bs)
- Enhancing toxicity of drugs, pollutants and other toxins by alcohol
- Alteration of metabolism of proteins, carbohydrates and lipids in the body

Acetaldehyde is one of the most toxic alcohol by-products, with the ability to alter protein structures. Acetaldehyde-altered proteins are responsible for many autoimmune reactions. Patients with neuro-psychological problems are commonly found to have antibodies against their own tissues.

2) Clostridia neurotoxins
Many Clostridia species normally colonise the human gut, e.g. Clostridium tetani. They do us no harm because healthy gut flora controls them. They produce powerful neurotoxins, which in a person with abnormal gut flora get absorbed through the damaged gut lining and cross the blood-brain barrier, affecting the patient's mental functioning. Many other species of Clostridia (perfringens, novyi, septicum, histolyticum, sordelli, etc) produce toxins similar to tetanus toxin as well as other toxins. Dr. William Shaw at Great Plains Laboratories describes a number of autistic children who showed serious improvements in their development and biochemical tests while on anti-Clostridia medication, and slipping back into autism as soon as medication was stopped. Professor Gibson of Reading University has also identified Clostridia overgrowth in the gut of autistic children.

Broad-spectrum antibiotics do not affect yeasts and clostridia while killing beneficial gut bacteria. With every repeated antibiotic course these pathogens continue to multiply, because their guardians (the beneficial bacteria) were wiped out by the antibiotic.

3) Gluteomorphins and casomorphins, or opiates from gluten and casein
In gut dysbiosis, these proteins are not digested properly before being absorbed in chemical structures similar to opiates. There has been substantial research by Dohan, Reichelt, Shattock, Cade and others, where gluteomorphins and casomorphins were detected in the urine of patients with schizophrenia, autism, ADHD, depression and autoimmune conditions. These proteins pass the blood-brain barrier and block certain brain areas like opiates do, causing neurological and psychological symptoms.

There are many other toxins being studied. The mixture of toxicity in each patient can be individual and different. What they have in common is gut dysbiosis, establishing a link between the gut and the brain. Grouping these disorders under the Gut and Psychology Syndrome (GAPS)™, GAPS patients can present with symptoms of autism, ADHD, OCD, dyslexia, dyspraxia, schizophrenia, depression, bipolar disorder, sleep disorders, allergies, asthma and eczema in any possible combination. Re-establishing normal gut flora and treating the digestive system must be considered before other treatments.

This connection between the state of a patient's gut and functioning of the brain has long been known by medics. The father of modern psychiatry French psychiatrist Phillipe Pinel concluded in 1807: "The primary seat of insanity generally is in the region of the stomach and intestines." Long before him Hippocrates, the father of modern medicine had said: "All diseases begin in the gut!" The more we learn with our modern scientific tools, the more we realise just how right they were!

Irritable bowel syndrome: An interplay of the gut and brain [70-75]

By **Tay Jia Yuan**, Executive Editor

Irritable bowel syndrome (IBS) is the most commonly diagnosed functional gastrointestinal condition, affecting 7-21% of the general population. Symptoms can vary over time, with patients presenting with abdominal pain or discomfort, and altered bowel habits. In most patients, it is a chronic relapsing disease which can significantly reduce health-related quality of life and work productivity.

Considered a disorder of the microbiota-gut-brain axis, there is growing evidence of gut dysbiosis in IBS patients. Such alterations of the bacterial composition of the gastrointestinal tract can arise from enteric infections, antibiotic use, psychological illness (anxiety and depression) and stress, all of which are factors known to predispose individuals to IBS. For example, a reduction in *Lactobacilli* and *Bifidobacterium* was observed in patients with diarrhoea predominant IBS, whereas patients with constipation predominant IBS showed increase in *Veillonella* species.