Psychobiotics: bacterial hope for depression?

Mark Greener

Increasing evidence links the microbiome’s composition with several psychiatric and neurological diseases, including autism, schizophrenia, attention deficit hyperactivity disorder, Parkinson’s disease, Alzheimer’s disease and multiple sclerosis - Mark Greener investigates.

Traditionally, clinicians’ attitudes towards the 100 trillion bacteria harboured by the human body ‘oscillated between benign neglect and suspicious distrust’. After all, commensal bacteria can be a reservoir of antibiotic-resistant pathogens. But over recent years, researchers increasingly recognised that the ‘microbiome’ influences numerous aspects of human biology including digestion, the immune system, metabolic pathways and responses to certain drugs.

Now increasing evidence links the microbiome’s composition with several psychiatric and neurological diseases, including autism, schizophrenia, attention deficit hyperactivity disorder, Parkinson’s disease, Alzheimer’s disease and multiple sclerosis. The recognition of the microbiome’s potential importance inspired a new therapeutic strategy that uses ‘psychobiotic’ supplements containing live microorganisms to improve mental health. Indeed, a recent study offers ‘first evidence’ that probiotics may help reduce negative thoughts associated with sad mood.

More diverse than the rainforest

Basically, the human microbiome occupies five niches: the lower gastrointestinal tract, skin, mouth, nose and vagina. The lower gastrointestinal tract is the most diverse niche, being colonised with more than 30,000 different strains of bacteria. To put this in context, the ‘most generous estimates’ suggest that an acre of undisturbed tropical rainforest may contain 15,000 different species.

This diverse population of gastrointestinal bacteria releases numerous signalling molecules that may influence the brain and behaviour through immunological (cytokines), endocrinological (cortisol) and neural (the vagus nerve and enteric nervous system) mechanisms. For example:

• Certain gastrointestinal bacteria produce neurotransmitters – including gamma-aminobutyric acid (GABA), serotonin, catecholamines and acetylcholine – and their precursors, such as tryptophan. Neurotransmitters released by bacteria may, for example, induce epithelial cells to release molecules that modulate signalling in the enteric nervous system.
• Increases in pro-inflammatory cytokines seems to be associated with depression and some other psychiatric conditions. The composition of the microbiome can influence the balance of pro- and anti-inflammatory cytokines.
• The vagus nerve modulates gastrointestinal motility and conveys information from the gut to the brain. Stimulating the vagus also seems to be anti-inflammatory. Indeed, modulation of the vagus may be a common pathway for the actions of antidepressants, anxiolytics and psychobiotics.
• The gastrointestinal microbiome seems to be causally involved in the development of the hypothalamo-pituitary-adrenal (HPA) axis.
• Bacterial products, such as endotoxins produced by gram-negative bacteria, can influence mood and cognition by, for example, activating the immune system and directly stimulating receptors on glial cells.

Researchers are exploring the details of these and several other potential pathways that link the gut microbiome and brain. This article can only skim the surface of this research and the pathogenic and therapeutic implications – several insightful recent reviews offer more detail.

Transplanting depression

While many of the details await further research, there seems little doubt that the gut microbiome influences the brain and behaviour. Depressed patients, for example, show marked changes in the composition of their gastrointestinal microbiome. Transplanting this abnormal microbiome may even ‘transplant’ depression.

For instance, researchers transplanted faecal microbiota from 34 depressed patients and 33 healthy controls into rats who had their gastrointestinal bacteria depleted with a cocktail of antibiotics. Rats that received a transplant from depressed patients showed a dysregulated microbiota and exhibited anhedonic and anxiety-related behaviours compared with those who received a transplant from controls. Against this background, probiotics are attracting increasing interest as a means to
restore a beneficial microbiota and influence behaviour.

For instance, mice raised in sterile environments lack a microbiome. The germ-free mice showed exaggerated physiological reactions to stress compared to normal controls. Colonising the gut using probiotics reversed this exaggerated stress response. Indeed, several researchers have shown that, in animal models at least, chronic administration of probiotics can reduce anxiety-like and depressive-like behaviours. Probiotics also normalise physiological changes linked to these behaviours, such as altered immune function and changes in levels of corticosterone, noradrenaline and brain-derived neurotrophic factor (BDNF), which is important for learning and memory.

Anxiety and depression seem to be associated with reduced levels of BDNF. For example, in preclinical studies the *Bifidobacterium longum* 1714 strain selectively improves stress-related behaviours, physiology and cognition. Similarly, in stress-sensitive mice, *Lactobacillus rhamnosus* JB-1 reduced anxiety-like behaviour in the elevated plus maze, despair-like behaviour in the forced swim test and stress-induced corticosterone levels. *L. rhamnosus* JB-1 also enhanced learning in a fear conditioning model, increased GABA levels in the brain and modulated expression of GABA<sub>A</sub> and GABA<sub>B</sub> receptors.

**Human studies**

More recently, evidence emerged that some probiotics induce beneficial changes in humans, although further studies are needed. For instance, one study enrolled 22 healthy volunteers, who received placebo and then *B. longum* 1714 daily both for four weeks. The volunteers underwent the socially evaluated cold pressor test, which combines psychological and physiological stress, at baseline and after treatment. *B. longum* 1714 seemed to attenuate the increases in cortisol and subjective anxiety induced by the cold pressor test compared with placebo. Consuming the psychobiotic also seemed to reduce daily stress reported by the volunteers.

In addition, the psychobiotic was associated with ‘subtle improvements’ in visuospatial memory that depended on the hippocampus and enhanced electroencephalographic activity in the prefrontal cortex, which, among other functions, is also involved with memory. The authors concluded that consumption of *B. longum* 1714 ‘is associated with reduced stress and improved memory’.

Further research needs to unravel the mechanisms through which *B. longum* 1714 might modulate stress and cognition. For example, the reduction in daily and acute stress may underlie the improved visuospatial memory. In addition, the psychobiotic seems, in animal models, to increase BDNF levels and stimulate neurogenesis. Further studies could ascertain if the same applies to humans.

Probiotics’ effects on stress and cognition may, however, be specific to each strain. For instance, as mentioned above, *L. rhamnosus* JB-1 showed promising effects in mouse models. But when researchers assessed four weeks treatment with *L. rhamnosus* JB-1 in 29 healthy volunteers, the probiotic did not alter stress-related outcomes, HPA response, inflammation or cognitive performance compared with placebo.

In other words, promising results in animal models may not always translate into clinical benefits. Several factors probably contribute to the discordance. For example, mice and humans differ in their gut microbiota. So mice and humans might also react differently to probiotics. Moreover, the inherently anxious strain or the imposition of chronic stress to promote anxiety may mean the mice react differently to healthy humans.

Some researchers suggest that combining species of probiotics may increase effectiveness by, for example, colonising different niches. So a recent Dutch study assessed a probiotic containing *Bifidobacterium bifidum* W23, *Bifidobacterium lactis* W52, *Lactobacillus acidophilus* W37, *Lactobacillus brevis* W63, *Lactobacillus casei* W56, *Lactobacillus salivarius* W24 and *Lactococcus lactis* (W19 and W58).

The study enrolled 40 healthy people without mood disorders who took the probiotic or placebo once daily for four weeks. Compared with placebo, those who received the probiotic showed significantly reduced overall cognitive reactivity to sad mood on the the revised Leiden index of depression sensitivity (LEIDS-r) scale, a trait that indicates vulnerability to depression.

Reductions in rumination and aggressive thoughts accounted for most of the probiotic’s benefits. Each LEIDS-r subscale has a maximum score of 24. Baseline mean aggression scores were 8.80 and 8.68 in the placebo and probiotic arms respectively. After four weeks, the scores were 8.45 and 6.25 respectively. Baseline mean rumination scores were 11.75 and 11.20 in the placebo and probiotic arms respectively. After four weeks, the scores were 11.85 and 8.25 respectively.

The authors comment that as the study enrolled people with minimal to mild scores on the Beck Anxiety Inventory and the Beck Depression Inventory II, ‘it is not surprising ... that the beneficial effect of probiotics intervention was selective for cognitive reactivity to depression and not for self-report...’
symptoms of depression or anxiety’. Nevertheless, the authors concluded that: ‘These results provide the first evidence that the intake of probiotics may help reduce negative thoughts associated with sad mood’.5

Another approach uses prebiotics – in other words, nutrients that stimulate the growth or activity of specific bacteria. For instance, in mice a combination of the prebiotics fructo-oligosaccharide and galacto-oligosaccharide improved depression-like and anxiety-related behaviours that were induced by chronic psychosocial stress. In addition, the prebiotic combination reduced HPA activation and dysregulation of the microbiota associated with chronic stress. Galacto-oligosaccharide supplements also appear to attenuate the increase in cortisol on waking from sleep in healthy volunteers and shift attention from negative towards positive stimuli.3

Current studies of psychobiotics and prebiotics are, however, relatively small, with a short follow up and typically enrolled healthy volunteers. So while the results are promising, whether psychobiotics could become an adjunctive treatment for anxiety or depression remains moot. Initially, clinical studies could target disorders associated with stress-related changes in the brain-gut axis that have a cognitive component, such as irritable bowel syndrome (IBS). Indeed, people with IBS seem to show impaired visuospatial memory on the Paired Associate Learning (PAL) test. B. longum 1714 was associated with subtly improved PAL performance in healthy volunteers.4 Nevertheless, while further studies are needed, modulation of the gut microbiome seems to offer an exciting potential new approach to the management of several common neurological and psychiatric conditions.

Mark Greener is a freelance medical writer.

References