PSYCHOBIOTICS AS NEW TYPE OF BACTERIATHERAPEUTICAL DRUGS

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Psychobiotics were previously defined as live bacteria (probiotics) which, when ingested, confer mental health benefits through interactions with commensal gut bacteria.

The gut microbiome comprises all microorganisms and their genomes inhabiting the intestinal tract. It is a key node in the bidirectional gut–brain axis that develops through early colonisation and through which the brain and gut jointly maintain an organism's health. A pivotal study found that mice raised in sterile environments and therefore lacking indigenous bacteria (germ-free mice) showed exaggerated physiological reactions to stress compared to normal controls. The abnormal reactions were reversible through probiotic-induced bacterial recolonisation. This finding revealed the microbiome's causal involvement in the development of the hypothalamic–pituitary–adrenal (HPA) axis. Gut bacteria have since been found to participate in the regulation of varied and important physiological processes, including immunomodulation, adiposity, and energy balance as well as the electrophysiological activity of the enteric nervous system.

Probiotics, beneficial bacteria that yield positive health outcomes, have received particular attention, both in the popular press and from the research community. Here, we critically evaluate efforts to manipulate commensal gut bacteria with psychobiotics. These psychobiotics were first defined as probiotics that, when ingested in appropriate quantities, yield positive psychiatric effects in psychopathology. The bacteria most frequently exploited as probiotics are the Gram-positive *Bifidobacterium* and *Lactobacillus* families. *Bifidobacteria* and Lactobacilli do not possess pro-inflammatory lipopolysaccharide chains, and so their propagation in the gut does not trigger full-fledged immunological reactions. With the presence of

such bacteria, the immune system learns to distinguish to between pro- and anti-inflammatory entities and develops appropriate immunogenic responses by identifying pro-inflammatory elements as antigenic. It should be noted, however, that Gram-positive bacteria are not always beneficial, and some, such as the *Clostridia* family, may be pathogenic.

The definition of psychobiotics be expanded along two dimensions: First, research on healthy individuals is demonstrating that psychobiotic benefits need not be restricted to clinical groups. Second, include prebiotics in the definition of psychobiotics. Prebiotics are compounds that, when fermented in the gut, produce specific changes in bacterial composition or activity. Prebiotics support the growth of intrinsic commensal bacteria. The majority of prebiotic compounds examined for their neural effects are fructans and oligosaccharides (comprising three to nine saccharide units).

Much psychobiotic research is based on rodent models, which use rodent stress inductions and rodent behavioural tests to assess motivation, anxiety, and depression. Psychobiotics applied to rodent models of illness, infection, and neurodegeneration also provide early clinical insight into human diseases. The psychophysiological effects of psychobiotics fall into the following three categories: 1. Psychological effects on emotional and cognitive processes. 2. Systemic effects on the HPA axis and the glucocorticoid stress response, and inflammation which is often characterised by aberrant cytokine concentrations. Pro-inflammatory cytokines share a strong and well-studied positive association with psychiatric conditions such as depression. For example, injection of interferon-/, a pro-inflammatory cytokine, has been shown to induce depression, which can be alleviated through antidepressant action. 3. Neural effects on neurotransmitters and proteins. Relevant neurotransmitters include g-aminobutyric acid (GABA) and glutamate, which control neural excitation–inhibition balance. Proteins include brain-derived neurotrophic factor (BDNF), which plays a crucial role in learning and memory processes, including spatial learning, extinction of conditioned fear, and object recognition. BDNF is reduced in anxiety and depression, a reduction that is reversible through antidepressant action.

The mechanisms through which psychobiotics exert their effects have yet to be clearly defined and remain poorly understood. Though there are some studies that provide mechanistic insights for humans, the majority of research is based on rodent models. A crucial step in developing knowledge of the mechanisms lies in investigating how the microbiome and the brain communicate with one another.

Gut bacteria regulate electrophysiological thresholds in enteric nervous system neurons. Myenteric neurons are also in close proximity to the gut lumen, which would facilitate their contact with the microbiome. Recent evidence also indicates that the microbiome affects ion transport controlled by cyclic adenosine monophosphate (cAMP).

Gut bacteria also produce a range of neurotransmitters through the metabolism of indigestible fibres. These include dopamine and noradrenalin by members of the *Bacillus* family, GABA by the *Bifidobacteria* family, serotonin by the *Enterococcus* and *Streptococcus* families, noradrenalin and serotonin by the *Escherichia* family, and GABA and acetylcholine by the *Lactobacillus*. Though there is no direct evidence as of yet, it is likely that these neurotransmitters modulate synaptic activity in the proximal neurons of the enteric nervous system, and is an important avenue for future research.

The vagus nerve plays an essential and wide-ranging role in coordinating parasympathetic activity, including regulation of heart rate and gut motility. It possesses an abundance of sensory fibres, and is able to convey rich information on organ function throughout the body to the brain. Vagal activity is sensitive to nutrition, exercise, and stress.

Stimulating the vagus nerve exerts anti-inflammatory effects, and is used therapeutically for refractory depression, pain, and epilepsy. There is also evidence of both antidepressants and anxiolytics exerting vagal effects, suggesting that vagal modulation may be a common pathway for the effects of antidepressants, anxiolytics, and psychobiotics.

The human gut is incapable of digesting macronutrients such as plant polysaccharides. While these frequently appear in the diet, the human genome does

not code the requisite enzymes for their digestion, which are supplied by the microbiome. The metabolisation of these fibers produces short-chain fatty acids (SCFAs), including acetate, butyrate, lactate, and propionate. SCFAs enter the circulatory system through the large intestine, where the greater proportion are directed into the liver and muscle. Although it is unclear to what extent the small fraction of SCFAs crossing into the central nervous system modulates neurotransmission, there is some evidence for their psychotropic properties at pharmacological concentrations.

Conclusions. Microbiome controls the canonical aspects of CNS, immunity and behavior in norm and in pathology. Nevertheless, the details of the role of microbiome in CNS disorders are unknown. The microbiome study has a perspective for prognosis and therapy associated with CNS disorder. Probiotics and functional foods can affect the action of the intestinal microbe on the central nervous system and the brain function. Along with the diet, they can restore intestinal homeostasis to improve cognitive or emotional function, and can be used to prevent, treat neurological disorders and to maintain the function of the immune system in stressful subjects.

Literature

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