

Good bacteria for good mood: probiotics and the brain-gut axis interactions

To the Editor We are witnessing a tremendous progress in our knowledge of the role of microbiota in health and disease. The gut microbiota, which constitutes a diverse and dynamic ecosystem, is currently considered a “living organ” closely involved in the numerous aspects of normal host physiology. Some important therapeutic implications of the modulation of the gut microbiota with probiotics, mainly in gastrointestinal disorders, have been recently discussed in a comprehensive review by Tanriover et al.¹ In a short paragraph, the authors presented the potential role of intestinal dysbiosis in the pathophysiology of irritable bowel syndrome (IBS), which is supported by the positive effects of antibiotic, probiotic, and prebiotic manipulation of the gastrointestinal microflora on IBS symptoms. More than 40 probiotic intervention studies performed in IBS patients have been recently published and reviewed.²

While discussing the evidence and promises of probiotic use in various diseases, it seems important to highlight the particular role of probiotics in the field of neurogastroenterology. Stress-related disturbances within the brain-gut axis have been recognized as the underlying pathomechanism of functional gastrointestinal disorders such as IBS. A growing body of evidence indicates that the enteric microflora, both commensal and pathogenic organisms, greatly affects the brain-gut axis regulation leading to the coining of a new term: the brain-gut-enteric microbiota axis.³ The intestinal microbiome and probiotics can significantly modulate the brain-gut axis communication, affecting not only the intestinal barrier and the enteric nervous system, but also altering brain functions. The bidirectional communication between the gut bacteria and the brain can occur through the neural, immune, and endocrine pathways.³ At the peripheral level, probiotics can affect the intestinal luminal milieu, gut permeability, and activation of the mucosal immune system. Additionally, they can also exert direct effects on the enteric nervous system and the gut sensory-motor function. Importantly, at the central nervous system level, certain probiotics can affect emotional processing, behavior, or memory function and even modulate

the central mechanisms of food intake contributing to obesity and metabolic disorders.⁴

Behavioral studies in germ-free animals indicate that microbiota can alter brain neurochemistry that is relevant for mood and that an individual's microbiota composition may affect susceptibility to anxiety and depression.⁴ Recently, antidepressant and anxiolytic-like properties of the probiotic bacterium, *Lactobacillus rhamnosus*, have been demonstrated in mice. The involvement of the vagus nerve and the central γ -aminobutyric acid system in the modulation of emotional behavior has also been shown.² Proliferation of *Lactobacilli* and *Bifidobacteria* residing in the mouse gut may also increase nonanxious behavior independently of the vagus nerve, possibly via bacteria-derived neuroactive substances. There is some evidence that *Bifidobacterium infantis* can alter the metabolism of tryptophan, a precursor to numerous biologically active agents, including serotonin as a main neurotransmitter of the brain-gut axis and mood regulator.⁵ Of note, probiotics can induce changes in the central nervous system gene expression, as *Bifidobacterium longum* has been demonstrated to affect mRNA expression of the hippocampal brain-derived neurotrophic factor. Additionally, bacteria may affect host behavior through the activation of the mucosal immune system resulting in cytokine-induced sickness behavior with neurovegetative and psychological components, which can lead to depression, anxiety, and cognitive dysfunction. In fact, epidemiological studies confirm the higher rates of psychological comorbidities in patients with IBS.²

Stress-related disturbances along the brain-gut-microbiota axis is another extensively studied research area in neurogastroenterology.⁶ Stress hormones affect the gut microbiota composition and, conversely, the gut microbiota can modulate stress response. Colonization with common commensals during the postnatal period plays a critical role in the development of stress response later in life. The gut microbiota modifying the expression of a variety of genes can act as a potential epigenetic factor programming the hypothalamic-pituitary-adrenal (HPA) axis response to stress. Experimental studies have shown that early

developmental trauma, possibly associated with dysbiosis, decreases glucocorticoid receptor expression by hypermethylation of a key regulatory component and, in consequence, affects the feedback regulation of the HPA axis with an impact on the endocrine/behavioral adaptation and susceptibility to stress-related disorders.⁶ Probiotics may reverse stress-induced visceral hypersensitivity and modulate the HPA axis reactivity as well as complex psychoneuroimmune interactions. Elucidation of the mechanisms underlying the brain-gut-microbiota axis interactions and central effects of probiotics may be of paramount importance regarding therapeutic implications for a wide spectrum of stress-related disorders far beyond the gut.

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Authors' reply We have read Dr Mulak's letter on the interaction of probiotics and the brain-gut-microbiota axis. We would like to thank for this valuable contribution and the very recent references cited about the topic.

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