Gut bacteria and brain function: The challenges of a growing field

In a recent article, Bravo et al. (1) demonstrated antidepressant and anxiolytic-like properties of a probiotic *Lactobacillus rhamnosus* in mice. Evidence for an involvement of the vagus nerve and the central gamma-aminobutyric acid (GABA) system in the modulation of emotional behavior by these bacteria was also provided. Overall, this is a commendable piece of work that has made an early and significant contribution to the increasingly fashionable exploration of, what the authors refer to as, the microbiome–gut–brain axis. However, this is just one story.

Earlier, Bercik et al. (2) showed that the proliferation of *lactobacilli* and *bifidobacteria* naturally residing in the mouse gut also increased non-anxious behavior, but independently of the vagus nerve. The possibility that bacteria-derived neuroactive substances were involved was suggested and has precedents (2). It is likely, therefore, that research in this field is destined to be fraught with complexities such as these. So, what are the research priorities and the possible strategies that will reveal the full therapeutic potential of nurturing gut bacteria?

Essential behavioral studies may initially benefit from using selective antimicrobials (2) and prebiotics (nutrients for gut bacteria) (3) to increase all strains of *lactobacilli* and *bifidobacteria* indigenous to the gut. That way, a broad range of microbes with psychotropic properties will be at optimal density and may influence more than emotional processing. Studies have shown that protein-induced proliferation of gut bacteria in mice augments spatial memory (4), and the ingestion of probiotic mixtures by healthy volunteers improves problem-solving abilities and has anxiolytic actions (Bravo et al., ref. 35). Prebiotic or antimicrobial-mediated production of microbiota influencing the vagus nerve might not just affect mood but might also lower the propensity for brain seizures, because vagus nerve stimulation has therapeutic benefits in epilepsy (5). Thus, prebiotic or antimicrobial administration and the evaluation of a battery of behaviors and neurophysiological outputs, in healthy animals and humans and in several brain disorders (in the presence of conventional therapies), are worthwhile pursuits.

Elucidating the mechanisms underlying the central effects of gut bacteria is important because it may lead to the discovery of alternative pathways and substrates to treat brain disorders that do not always respond to prescribed drugs. Comparing the genetic composition of bacteria linked to vagus activity (*L. rhamnosus*) (1) with that of one which is not (*bifidobacterium*) (2) and with that of one without psychotropic properties at all (*Lactobacillus salivarius*) (1) would help identify the microbial components that influence the brain. Bacterial gene profiling by the Human Microbiome Project at the National Institutes of Health has been active since 2008 and promises to yield sufficient information to allow such comparisons to be made.

In summary, investigations into the microbiome–gut–brain axis have already yielded compelling evidence for the link between gut bacteria proliferation and brain function. Although understanding the mechanisms underlying the psychotropic effects of single probiotics is important, the use of prebiotics and antimicrobials in research will reveal whether growth of all *lactobacilli* and *bifidobacteria* strains is a viable strategy to treat several brain disorders, particularly when used adjunctively with conventional medications.

Philip W. J. Burnet
University Department of Psychiatry, Warneford Hospital, Oxford OX3 7JX, United Kingdom


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1E-mail: phil.burnet@psych.ox.ac.uk.