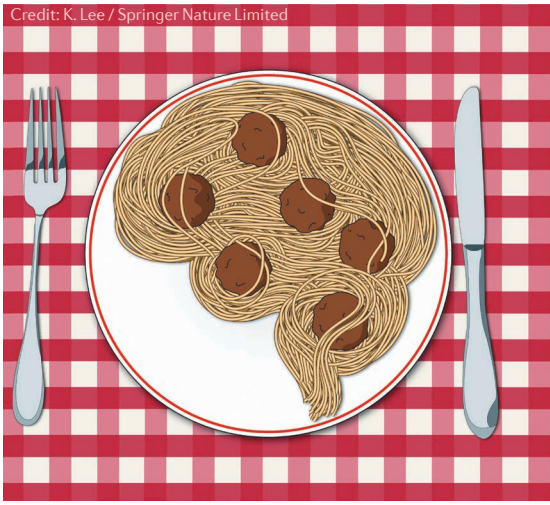
MILESTONE 18

The microbiota–gut–brain axis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A link between the gut microbiota and the brain has long been surmised, but in recent decades, studies have started to report causal effects of the gut microbiota on our brains and behaviour, and the underlying molecular mechanisms have begun to be elucidated.

Several early studies in animal models provided evidence that stress can perturb the composition of the gut microbiota and that enteric pathogens can affect host behaviour. In 2004, a study showed that germ-free (GF) mice exhibit an upregulated hormonal response to stress induced by physical restraint, implying that the microbiota influences the neuroendocrine hypothalamic–pituitary–adrenal (HPA) axis, the central stress response system. However, the effects of the microbiota — or the absence thereof — on behaviour remained unclear. Seven years later, in 2011, several experimental findings in mice shed light on how a lack of conventional microbiota affects behaviour, gene expression in the brain and the development of the nervous system.

Studies revealed that GF and antibiotic-treated mice displayed reduced anxiety-like behaviour compared with specific pathogen-free (SPF) controls. For example, GF mice were found to spend more time on the open arms of the elevated plus maze (EPM), and in the illuminated compartment of the light–dark box, than their SPF counterparts. The offspring of GF mice that had been conventionalized with SPF microbiota, but not GF mice conventionalized as adults, showed behaviour similar to SPF controls, suggesting that the microbiota may influence the brain during a 'critical period' of development.

Related work showed an effect of differences in gut microbiota on behaviour. Mice treated with a mixture of antimicrobials (ATM) showed more exploratory behaviour, and GF BALB/c mice (which are typically timid) colonized with microbiota from another mouse strain exhibited more exploratory behaviour than those receiving BALB/c microbiota, and vice versa. Furthermore, it was found that treatment of SPF mice with the probiotic *Lactobacillus rhamnosus* (JB-1) reduced anxiety- and depression-like behaviour.

As well as behavioural differences, the brains of animals with altered or absent gut microbiota displayed various molecular differences. These included brain-region-specific changes in levels of brain-derived neurotrophic factor (BDNF; which is known to be modulated in anxiety and depression), differences in the expression of various neurotransmitter receptors and alterations in the turnover of certain neurotransmitters, including serotonin.

Indeed, much research since has focused on serotonin as a node of gut microbiota–brain interactions. Spore-forming gut bacteria were found to drive the production of serotonin by enterochromaffin cells in the mouse colon, although exactly how this may affect the brain has not been clear. Moreover, male (but not female) GF mice show higher levels of hippocampal serotonin and plasma levels of a serotonin precursor, suggesting that certain influences of the gut microbiota on the brain may be sex-specific.

How the gut microbiota signal to the brain has been the focus of much research. Evidence from models of multiple sclerosis and stroke suggested that changes in the gut microbiota may indirectly influence the central nervous system via effects on immune homeostasis and immune responses. In support of a vagus-nerve mediated route for gut-derived signals, severing the vagus nerve below the diaphragm blocked the anxiolytic and gene expression effects of *L. rhamnosus* (JB-1). By contrast, ablating the vagus nerve or sympathetic nerves did not prevent the effects of ATM on anxiety-like behaviour, and ATM-treated mice showed no overt signs of gut inflammation or alterations in enteric neurotransmitter levels, indicating that some gut–brain communication routes might be independent of the immune and nervous systems.

In fact, later research has started to uncover other means of gut–brain communication — in particular, microorganism-derived products that can directly or indirectly signal to the nervous system. For example, the offspring of immune-challenged mice showed gut dysbiosis, disrupted intestinal integrity and behavioural abnormalities (including anxiety-like behaviour), as well as high serum levels of a microbial metabolite that, when injected into wild-type mice, induced anxiety-like behaviour. Similarly, in a model of Parkinson disease (a neurological disorder associated with α-synuclein aggregation in the brain) the presence of gut microbiota or microbially produced short-chain fatty acids promoted neuroinflammation, motor impairments and α-synuclein pathology.

Nearly all of the work in this field to date has been carried out in animal models, and establishing whether those findings translate to humans will be crucial yet challenging. As an example of such an endeavour, a study investigated the link between faecal microbiota composition and quality of life using data from more than 1,000 people. As well as identifying bacterial genera associated with higher quality of life or depression, they carried out metagenomic analyses that indicated that the potential of microorganisms to synthesize certain neuroactive metabolites may also correlate with mental wellbeing.

Together, the studies described above have laid the foundations for our understanding of the effects of the gut microbiota on the brain and behaviour, and the mechanisms that underlie them, and represent initial efforts to explore the relevance of animal-model findings for humans.

Natasha Bray, *Nature Reviews Neuroscience*

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