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GUT MICROBIOTA

Host–microbe interactions and the enteric nervous system: a new connection?

The gut microbiota can influence host serotonin (5-HT) biosynthesis in the gut via microbial-derived metabolites, according to new research published in *Cell*. The findings add further weight to the concept of a microbiota–gut–brain axis and its influence on gastrointestinal homeostasis.

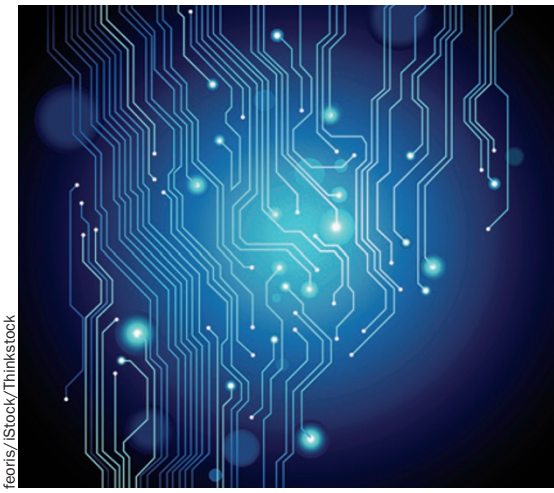
How the gut microbiota communicates with the nervous system is an active area of research, with studies investigating both the central nervous system and the enteric nervous system, our so-called second brain. "In this most recent project, we explored the notion that indigenous gut microbes could modulate levels of neurotransmitters in the host, and that this action might be one way by which microbes communicate with the nervous system," explains author Elaine Hsiao (California Institute of Technology, USA). Hsiao and colleagues focused their latest research efforts on gut-derived 5-HT, which is a key signalling molecule with a fundamental role in gastrointestinal motility and haemostasis.

A series of experiments were conducted in germ-free mice and mice colonized by bacteria (specific pathogen-free [SPF] mice) as well as cell cultures. Compared with SPF mice, germ-free mice had markedly decreased levels of colonic and faecal 5-HT. The researchers demonstrated that the gut microbiota can promote 5-HT biosynthesis in colonic enterochromaffin cells in mice by enhancing expression of *Tph1* (encoding tryptophan 5-hydroxylase 1, the rate-limiting enzyme for mucosal 5-HT biosynthesis). Importantly, 5-HT deficiency in germ-free mice could be corrected by postnatal colonization with SPF; moreover, colonic 5-HT biosynthesis could be reduced by antibiotic treatment in SPF mice.

Interestingly, specific spore-forming bacteria (dominated by Clostridia) from both mice and human microbiota samples were found to regulate 5-HT levels, coinciding with increased *Tph1* expression. The investigators also provide evidence that the microbiota-dependent changes in 5-HT levels seem to affect gastrointestinal motility (transit time and activation of enteric neurons) and platelet function (activation and aggregation).

Finally, the researchers established that microbial metabolites conferred the serotonergic effects of the gut bacteria. Metabolomic profiling revealed that colonization of germ-free mice with mouse-associated spore-forming bacteria leads to notable alterations in 75% of the 416 metabolites detected; similar changes were observed when colonizing with human-associated spore-forming bacteria. To identify specific 5-HT-regulated metabolites, a subset of biochemicals identified during metabolic profiling and several short-chain fatty acids previously shown to be produced by spore-forming bacteria (acetate, butyrate and proprionate) were tested for their ability to induce 5-HT production *in vitro* and *in vivo*. Several metabolites (including butyrate, deoxycholate and α-tocopherol) increased 5-HT production in enterochromaffin cells *in vitro*, which corresponded with increased *Tph1* expression. A similar transient increase in colonic and serum levels of 5-HT was observed upon injection of some metabolites (including deoxycholate and α-tocopherol) into germ-free mice.

"This is an important study because it provides additional support for the concept that gut microbes can influence neuronal–hormonal signalling in our gastrointestinal tract and beyond," says Gary Mawe (University of Vermont, USA) who was not involved in the new research. He points out that the experimental conditions used, particularly the use of germ-free mice, are more 'extreme' than the scenario in humans, which is an important factor when trying to translate these findings to humans. "One of the consistent features of effective microbiotic influence on neuronal–hormonal signalling in mice, including those reported in this study, is that it seems to be limited to a critical period that includes animals that are ≤10 weeks of age," he adds. "If treatments are to be developed for adult humans, they will probably involve responses that are not restricted by this developmental limitation."



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The researchers plan to explore whether there might be any therapeutic potential in manipulating the gut microbiota (and therefore microbial by-products) to promote serotonin biosynthesis. "We are particularly interested in investigating whether microbial modulation of host neuroactive molecules influence neurodevelopment, brain activity and/or behaviour," says Hsiao, "and how neuroactive molecules, like serotonin, might influence the gut microbiota." More research is needed to clarify how microbiota-based control of serotonin biosynthesis and interactions with the enteric nervous system influence gastrointestinal health and disease.

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Original article Yano, J. *et al.* Indigenous bacteria from the gut microbiota regulate host serotonin biosynthesis. *Cell* **161**, 264–276 (2015)