Gut microbes alter fly walking activity

A gut bacterium has been found to modulate locomotor activity in the fruit fly Drosophila melanogaster. This effect is mediated by the level of a sugar and the activity of neurons that produce the molecule octopamine. See Letter p.402

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Is the refrain that “my microbes make me do it” true? Scientific reviews and the popular press often report that microbes can influence many aspects of the behaviour of their healthy animal or human hosts, from cognition to social interactions to emotional state. If this is true, perhaps future microbial-based therapies might be used to improve mental health. Yet the evidence for most of these claims of microbial effects is limited. Experiments are urgently needed that definitively test whether bacteria can have a causal role in behaviour, and that identify the underlying mechanisms. On page 402, Schretter et al. provide a superb example of rigorous scientific analysis, in which they demonstrate that the walking activity of the fruit fly Drosophila melanogaster can be affected by a specific gut bacterium. The authors identify a bacterial enzyme that mediates this effect, and establish aspects of the mechanism by which the fruit fly responds to the bacterium.

Schretter et al. used standard techniques to analyse the bacterial residents of the gut. The authors compared walking activity in flies harbouring their natural gut microbes (the microbiota) and flies that had been treated to eliminate the gut bacteria, and they observed that the treated flies were hyperactive in comparison to the others. These hyperactive flies walked faster and for longer than the others, but their daily (circadian) rhythms of activity and sleep were not perturbed. To determine the microbes associated with this effect, Schretter et al. supplied the hyperactive flies with various bacteria, and found that the bacterium Lactobacillus brevis restored walking activity to the level observed in flies that retained their complete microbiota.

There is a common expectation that gut microbes influence animal behaviour by producing small metabolites, including neurotransmitter molecules, which interact directly with the nervous system in the gut or that enter the bloodstream and from there reach the brain. However, the bacterial product identified by Schretter and colleagues as involved in walking behaviour does not fit this paradigm. The authors provide persuasive evidence that the presence of the sugar-modifying enzyme xylose isomerase, which is produced by L. brevis, reduces locomotor activity in D. melanogaster (Fig. 1). Further experiments revealed that supplying xylose isomerase to flies whose bacteria had been eliminated was necessary and sufficient to modulate fly locomotion.

How does xylose isomerase cause D. melanogaster to slow down? The enzyme mediates the interconversion of certain sugar molecules — the change of glucose into fructose, for example. Schretter and colleagues found that the flies treated to remove their gut bacteria have a higher level of the sugar trehalose than do those that retain their usual microbiota. Perhaps this means that xylose isomerase decreases the availability of a glucose substrate needed for the synthesis of trehalose. The authors administered trehalose to flies that lacked gut bacteria and had been provided with xylose isomerase, and report that the trehalose treatment caused the flies’ walking speed to increase.

The authors proceeded to investigate the neural basis of the hyperactivity phenomenon. They used genetic approaches to activate neurons that regulate locomotion in D. melanogaster and the results focused their attention on a type of neuron called an octopaminergic neuron, which produces the neurotransmitter molecule octopamine. Schretter et al. found that the walking activity of flies that lacked gut bacteria but had been given xylose isomerase was increased by activation of the genes encoding enzymes needed for the synthesis of octopamine. Such an effect on locomotion was not observed for other neurotransmitters they tested. Furthermore, the authors observed that the flies with their natural microbiota and those that had been treated to remove gut bacteria but had received xylose isomerase both walked faster if they received octopamine.

Octopamine is a well-characterized regulator of locomotion in flies. In vertebrates, the neurotransmitter molecule noradrenaline, which is related in structure to octopamine, fulfils a similar role in promoting physical activity. Work remains to be done to fill in the gaps in explaining how xylose isomerase affects the level of trehalose in the fruit fly and the activity of octopamine-producing neurons in the brain. Nevertheless, one key conclusion emerges: the effect of bacterial products on fly locomotion is mediated by the level of a sugar and the activity of neurons that produce the molecule octopamine.
A back door to improved health

The coenzyme NAD\(^+\) can be produced from the amino acid tryptophan. It emerges that inhibiting an enzyme that degrades an intermediate in this pathway can help to combat kidney and liver diseases in mouse models. See Article p.354

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Throughout the history of life on Earth, there has been a requirement for small molecules called nucleotides. Long chains of nucleotides make up the genetic code, and single nucleotides transduce signals or transfer energy. In addition, a dimeric form of nucleotide called nicotinamide adenine dinucleotide (NAD\(^+)\) serves at least two pivotal cellular functions. The first is to shuttle high-energy electrons to enzymatic complexes found in organelles called mitochondria, where their energy can be efficiently harvested; the second is as a substrate for enzymes such as sirtuins, which regulate many cellular behaviours. On page 354, Katsyuba et al.\(^1\) shed light on a fundamental mechanism by which the correct levels of NAD\(^+)\) are maintained in cells, and demonstrate how augmenting this pathway can affect disease.

In simple terms, the available pool of NAD\(^+)\) in a cell is governed by the balance between its generation and its consumption. The predominant pathway by which NAD\(^+)\) is generated in rodents relies on the recycling of a molecule called nicotinamide (Nam) that is either ingested or released by enzymes that consume NAD\(^+)\) (Fig. 1). There are several other routes of NAD\(^+)\) production, including a de novo synthesis pathway that starts with the essential amino acid tryptophan (Trp)\(^2\). Mutations that disrupt the enzymes responsible for converting Trp to NAD\(^+)\) result in multi-system developmental alterations in humans\(^3\), demonstrating the importance of this de novo pathway.

Katsyuba et al. set out to study \(\alpha\)-amino-\(\beta\)-carboxymuconate-\(\varepsilon\)-semialdehyde (ACMS), an unstable and little-studied intermediate of the Trp pathway. ACMS can either spontaneously convert to the next intermediate on the path to NAD\(^+)\) or can be degraded by a train of enzymes, starting with ACMS decarboxylase (ACMSD). As such, ACMSD would be predicted to limit the amount of NAD\(^+)\) produced through de novo synthesis. ACMSD is evolutionarily conserved from the nematode worm <i>C. elegans</i> to mice\(^4\) — an observation that is striking because, until recently, nematodes were not thought to synthesize NAD\(^+)\) de novo.

The authors inhibited the acsm-1 gene, which encodes the equivalent of ACMSD in nematodes. This inhibition did increase NAD\(^+)\) levels. Increasing NAD\(^+)\) is well known to extend lifespan in worms, and the authors found that lifespan was longer in the worms in which acsm-1 expression was completely blocked. Moreover, preventing acsm-1 expression led to molecular responses that have been linked to defence against ageing\(^5,6\): increased activation of the sirtuin enzyme sir-2.1; enhanced mitochondrial function; and a protective mitochondrial stress response.

In mice and humans, ACMSD is most highly expressed in the liver and kidney\(^7\), and a recent study indicates that these are the main organs for Trp-dependent NAD\(^+)\) generation\(^8\). Katsyuba et al. found that inhibition of the Acmsd gene increased NAD\(^+)\) levels in mice and nematode worms, and improves outcomes in mouse models of liver and kidney diseases.

**Figure 1 | NAD\(^+)\) biosynthesis in disease.** When the coenzyme nicotinamide adenine dinucleotide (NAD\(^+)\) is consumed by enzymes, nicotinamide (Nam) is generated as a reaction product. Through a recycling mechanism called the salvage pathway, NAD\(^+)\) can then be regenerated. Nam salvage is considered the predominant mechanism for NAD\(^+)\) biosynthesis, but NAD\(^+)\) can also be generated through multiple other routes. One of these is the de novo pathway, whereby the amino acid tryptophan (Trp) is converted to NAD\(^+)\) through several intermediates, including \(\alpha\)-amino-\(\beta\)-carboxymuconate-\(\varepsilon\)-semialdehyde (ACMS). This pathway can be depleted by the enzyme ACMS decarboxylase (ACMSD), which degrades ACMS to picolinic acid (Pic). Katsyuba et al.\(^3\) report that chemical inhibition of ACMSD raises NAD\(^+)\) levels in mice and nematode worms, and improves outcomes in mouse models of liver and kidney diseases.