News & views

Microbiology

Gut microbes shape athletic motivation

Gulistan Agirman & Elaine Y. Hsiao

Microorganisms in the gut produce molecules that activate sensory neurons, stimulating exercise-associated reward circuits in the brain. This newly discovered pathway in mice affects motivation for prolonged exercise. See p.739

Thousands of studies have established that routine physical activity lowers the risk of chronic illness, improves cognitive function and decreases overall mortality. The best health outcomes are associated with exercise in the form of prolonged and recurrent training sessions[1]. If the health benefits of exercise are undisputable, then why do so many people adopt a sedentary lifestyle? A lack of motivation or an intolerance to physical exercise are often the culprits, and some suggest that a shift in mindset would be enough to take up daily exercise[2]. However, Dohnalová *et al.*[3] report on page 739 that the motivation to perform long-term physical activities in mice is not exclusively driven by the brain but is, in fact, underpinned by the input of gut bacteria.

The authors' findings point to new considerations regarding factors that can enhance physical performance. If these findings are relevant to humans, they raise the question of whether targeting gut bacteria could improve the mental processes associated with the decision to exercise across individuals, whether elite athlete or not.

Aside from the physiological role of intestinal microorganisms (also known as the gut microbiome) in energy metabolism[4], specific bacterial groups have also emerged as key regulators of exercise performance. This occurs through the production of molecules that can be used to generate energy, or by aiding the clearance of molecules associated with physical exhaustion in the host[5,6]. But whether intestinal microbes engage brain circuits involved in the execution of physical activity was unknown until now.

Dohnalová *et al.* ranked a large group of mice according to the animals' performances when running on treadmills or wheels. The authors then profiled a variety of physiological parameters, including genetic signatures; molecular profiles in blood serum; metabolic parameters; and the microbial repertoire in the gut. The composition of the bacterial community alone predicted running capacities with high accuracy, suggesting that gut bacteria drive exercise performance. Indeed, depleting gut bacteria through antibiotic treatment decreased athletic endurance. By contrast, transferring the gut microbiome from high-performing mice into germ-free mice, which are raised devoid of microbial colonization of their gut, increased the recipients' running capacities to a level that matched that of the microbial-sample donor.

Motivation of actions is governed in the central nervous system and involves signalling mediated by the molecule dopamine[7]. Dopamine-producing neurons from brain regions called the ventral tegmental area and the substantia nigra project to several other brain regions to regulate cognitive, emotional and motivational aspects of reward-associated behaviours[7]. To identify mechanisms connecting gut bacteria to physical performance, Dohnalová *et al.* profiled the type of neuron and the corresponding molecular changes affected by the presence and the absence of gut microbes (Fig. 1).

The authors report that in mice harbouring a typical microbiome, exercise decreases the expression of the enzyme monoamine oxidase (MAO), which degrades dopamine

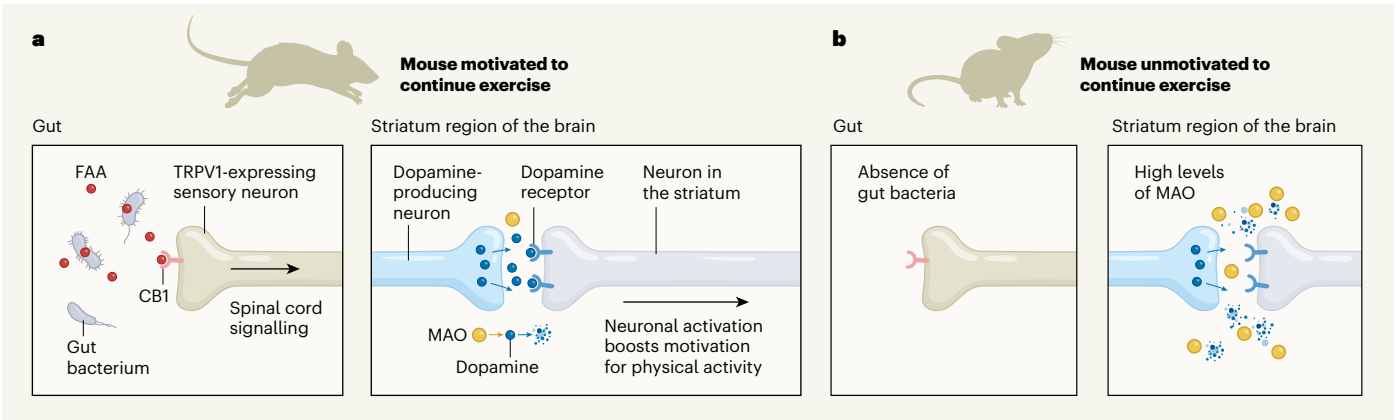

Figure 1 | A pathway from gut microbes to the brain regulates the motivation to exercise. a, Dohnalová *et al.*[3] report that certain gut bacteria in mice produce molecules called fatty acid amides (FAA), which bind to the cannabinoid 1 receptor (CB1) and thereby activate sensory neurons in the gut that express the protein TRPV1. These neurons connect to the brain through the spinal cord. Activation of these neurons results in decreased expression of the enzyme monoamine oxidase (MAO) in the striatum region of the brain; this enzyme can degrade dopamine and other neurotransmitter molecules. Dopamine-producing neurons induce an exercise-dependent surge of the molecule, which then activates neurons in the striatum that have dopamine receptors. This triggering of neuronal activity in the striatum aids the motivation for exercise. **b**, In the absence of gut bacteria, the sensory neurons in the gut are not excited. The level of MAO then remains high, which blunts dopamine signalling in the striatum and results in a premature termination of physical exercise.

and some other neurotransmitter molecules. Dohnalová and colleagues also found that the exercise-induced burst of dopamine activates specific neuronal cell types in a region of the brain called the striatum. Inhibition of dopamine-producing neurons in the ventral tegmental area or blockade of dopamine sensing reduced athletic endurance, indicating that the exercise-induced dopamine surge and subsequent neuronal activity in the striatum are crucial for willingness to maintain body movement. However, when mice lacking gut bacteria exercised, the expression of MAO remained unchanged, and both the dopamine surge and the striatal neuronal activity were blunted compared with what happens in mice that have gut microbes. Restoration of the gut microbiome, inhibition of MAO and an artificially generated increase of dopamine signalling in the striatum were each sufficient to restore exercise performance in mice lacking gut bacteria.

The main communication routes between gut bacteria and the brain include: modulation of immune-system function, direct release of microbiome-produced molecules to the bloodstream and local stimulation of neurons that project to the central nervous system[8]. Dohnalová *et al.* demonstrate that the microbiome uses local neuronal stimulation to access motivational circuits in the brain. Specific sensory neurons — those that express the protein TRPV1, innervate the colon and project to the spinal cord — were stimulated after exercise in conventional mice, but not in those treated with antibiotics. Activation of these sensory neurons in bacteria-depleted animals resulted in restoration of physical performance, a decrease in MAO levels, a burst of dopamine and the triggering of neuronal activation in the striatum.

Furthermore, the authors found that bacterially produced molecules called fatty acid amides (FAA) could activate TRPV1-expressing sensory neurons, and that the abundance of FAA correlated with physical performance. Dietary supplementation of FAA and gut colonization of germ-free mice with FAA-producing bacteria each had the capacity to restore exercise-associated dopamine signalling in the brain and to improve physical performance. The authors discovered that FAA molecules acted on a receptor known as the cannabinoid receptor CB1, which is expressed by sensory neurons. Blockade of this receptor or of CB1-associated signalling inhibited the beneficial effect of FAA supplementation or of FAA-producing bacteria on physical activity.

Dohnalová *et al.* have demonstrated that the circuits involved in the motivation needed to sustain physical activity in mice are modulated by gut microbes. The evolutionary explanation for such regulatory control by microbes on the cognitive function of their host is puzzling. The trillions of microbes in the gut release and regulate a vast repertoire of molecules that can interact with functionally diverse classes of receptors in the host[9]. It is possible that the effect observed is a coincidence that occurs secondarily to the local gut functions of molecules produced by bacteria. Given that TRPV1-expressing sensory neurons also convey pain-related signalling, an alternative explanation might involve a beneficial interdependence in the relationship between gut health and the ability to engage in energy-consuming physical activities.

The psychotropic potential of the microbiome-derived molecules to target the brain, as highlighted by Dohnalová *et al.*, is of great interest for possible therapeutic options, if this phenomenon is also relevant to people. Beyond understanding the pathways that are valuable for encouraging physical activity, the study provides insight into non-invasive methods to access reward circuits in the brain, which are often dysregulated in addictive-behaviour disorders. Although tempting to consider the human implications of this research, gauging the practical relevance of these findings will require extensive further assessment. A variety of other factors influence motivational states in people, requiring a range of strategies to strengthen motivational and reward circuits in unfavourable environments.

Gulistan Agirman and **Elaine Y. Hsiao** are in the Department of Integrative Biology & Physiology, University of California, Los Angeles, Los Angeles, California 90095, USA.
e-mail: agirman@g.ucla.edu

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Medical research

Genetics and anatomy sculpt ovarian cancer

Denarda Dangaj Laniti & George Coukos

The therapeutic options available to treat ovarian cancer need improvement. Data that reveal the cellular, molecular and mutational landscape as such tumours grow and spread might aid efforts to develop new targeted therapies. **See p.778**

The most common type of ovarian cancer[1], called high-grade serous ovarian cancer (HGSOC), is challenging from a therapeutic perspective. By the time most individuals are diagnosed with this type of tumour, it has already spread (metastasized) from the primary site to distant regions, seeding cancer cells in multiple abdominal locations (intraperitoneal sites). At that point, symptoms arise because of an accumulation of peritoneal fluid in these areas. On page 778, Vázquez-García *et al.*[2] provide insights into metastatic ovarian cancer.

Key advances[3] have been made in understanding the molecular and genetic alterations that underlie the development of HGSOC, as well as in clarifying how these tumours are recognized by the host's immune system and in characterizing the immune cells in the tumour microenvironment (TME)[4]. However, such information comes mainly from analyses of single sites of tumour growth. Intratumoral heterogeneity, in terms of variation in the tumour cells and immune cells present, is highly prevalent in HGSOC[5], but the consequences of this remain unclear.

So far, variations in the TME cell types across intraperitoneal sites have been thought to arise in a random manner. Vázquez-García *et al.* attempt to decipher the pattern of this diversity. The authors gathered evidence that includes single-cell data on gene and protein expression, and assessed mutations across 160 tumour sites in 42 individuals with ovarian cancer who had not yet received treatment. The authors examined the primary site of tumour growth (the ovary or fallopian tube, or both) and sites to which the tumour had spread, such as the bowel and peritoneum (the membrane that lines the inner wall of the abdomen).

Applying mathematical models used in ecology to measure dissimilarities within and between individuals, the authors show that the TME's cellular constituents in this type of