Tidbits of Science

Gut microbes control our heart via the brain

Previously unknown gut-brain-heart axis could pave the way for treatments for high blood pressure and heart failure.



A metabolite produced by bacteria in our gut controls heart function via cells in the brain. A team from the Max Delbrück Center has described this previously unknown gut-brain-heart axis in Circulation Research. It points the way towards potential treatments for high blood pressure and heart failure.

Millions of people worldwide suffer from high blood pressure or heart failure. In many cases, the cause is diastolic dysfunction – brought about by an increasingly stiff heart muscle that finds it difficult to relax and fill completely with blood. Why the heart stiffens is not yet fully understood.

A team led by Dr Suphansa Sawamiphak, head of the Cardiovascular-Hematopoietic Interaction research group at the Max Delbrück Center, has now discovered that gut bacteria could play a crucial role in this disease process. In experiments using zebrafish as a model, the researchers discovered that certain microbes in the gut produce a small molecule called indole-3-acetic acid (IES) from the amino acid tryptophan. IES acts on neurons in the brain, which in turn control the heart. Sawamiphak and her colleagues describe this direct link between bacteria, the brain and the heart in the journal Circulation Research.

"We were surprised that a single bacterial metabolite can simultaneously influence the central nervous system, the heart and, moreover, key hormonal systems," says the study's lead author, Bhakti Zakarauskas-Seth from Sawamiphak's team. "This shows that the brain can act as a central hub in communication between the gut and the heart."

High blood pressure caused by overactive neurons

To understand how gut bacteria might influence the heart, the researchers focused on a group of neurons in the hypothalamus of zebrafish larvae that produce certain neuropeptides known as hypocretins (HCRT). These neurotransmitters, also known as orexins, regulate many involuntary functions in the body, such as sleep and eating behaviour, as well as heart activity. When IES levels fell in the zebrafish larvae, the HCRT neurons became overactive. This amplified their sympathetic nerve signals to the heart, causing the heart muscle to stiffen and reducing its ability to relax fully.

When the scientists administered IES to the larvae, neuronal activity returned to normal. Heart function and blood pressure improved, and even related hormones such as renin and angiotensinogen returned to healthier levels.

In the next step, Zakarauskas-Seth and her colleagues analysed data from a group of patients.

After all, we humans also possess HCRT neurons. The researchers found that IES levels were reduced in patients with high blood pressure. Notably, they observed a gender-specific effect: women with high blood pressure had significantly lower IES levels in their serum samples than men suffering from hypertension.

Prevention and treatment

Diastolic dysfunction is very common – almost half of all people over the age of 70 show at least mild symptoms. It is the cause of heart failure with preserved ejection fraction (HFpEF), which affects more than 50 percent of patients with heart failure.

For these people, the research findings open up several possibilities, says Zakarauskas-Seth: "IES levels could serve as a biomarker to identify patients at high risk of high blood pressure or heart failure. And from a therapeutic perspective, increased IES concentrations – achieved, for example, through diet, probiotics or dietary supplements – could represent a new strategy for preventing or treating cardiovascular diseases."

The fact that a single bacterial metabolite can influence the central nervous system, the heart and the endocrine system is an important message, adds Zakarauskas-Seth. "The body does not function in isolated compartments: gut health, microbial balance and diet have a direct impact on how well the heart functions." The researchers now intend to validate their findings in other animal models. Clinical trials will also be required to determine what actual benefits patients can derive from increased IES levels.

Live healthier, live longer

How risk factors affect life expectancy.



People aged 50 who do not smoke, have normal blood pressure, do not have high cholesterol levels or diabetes, and maintain a healthy body weight not only live longer but also remain free from cardiovascular disease for longer. This applies equally to women and men. However, even those who make changes later in life can still benefit. This is what scientists at the University Medical Center Hamburg-Eppendorf (UKE) have discovered in a large-scale study – in collaboration with around 120 researchers worldwide.

The findings were presented at the main conference of the American College of Cardiology and published simultaneously in the New England Journal of Medicine.

"The five classic risk factors – high blood pressure, smoking, diabetes, being underweight, overweight or obese, and high cholesterol levels – are responsible for around half of all cardiovascular diseases worldwide. We wanted to know how the absence or control of these factors affects life expectancy," says Prof. Dr Christina Magnussen, lead author and deputy director of the Department of Cardiology at the UKE.

The study shows that women who do not have any of these risk factors at the age of 50 develop cardiovascular disease on average 13.3 years later and die 14.5 years later than women with all five risk factors.

Men without these risk factors live 10.6 years longer without cardiovascular disease and die, on average, 11.8 years later than men with the risk factors. The risk factors themselves have varying significance; for example, women who do not smoke at the age of 50 live 5.5 years longer without cardiovascular disease, whilst for men the figure is 4.8 years.

Another important finding of the study is that behavioural changes are worthwhile even later in life. "Of all five risk factors, controlling blood pressure is linked to the greatest number of additional healthy years of life," says Prof. Dr Stefan Blankenberg, the study's senior author and Medical Director of the University Heart and Vascular Center at the UKE. People who bring their high blood pressure under control or give up smoking between the ages of 55 and 60 live longer and without cardiovascular disease than those who do not change their lifestyle.

The researchers analysed data from more than two million people across 39 countries for their study. This makes it one of the most comprehensive research projects to date on the impact of risk factors on life expectancy.

Why our immune system remembers vaccinations for decades

Metabolic quiescence is the key to long-lasting immunological memory.



Why is the human immune system often able to remember a vaccination for a lifetime? Researchers at Friedrich-Alexander University Erlangen-Nuremberg (FAU) and Erlangen University Hospital have explored this question, and their study provides a surprisingly clear answer: the immune cells responsible for immunological memory switch to a kind of standby mode at an early stage. They can survive for many decades in this state. The findings have now been published in the journal *Nature Immunology*.

The research team used the yellow fever vaccine as a model system. And with good reason, as it is considered one of the best examples of an effective vaccine in humans: for most people, it requires just a single injection. Nevertheless, its protective effect is exceptionally strong and often lasts a lifetime. This makes the vaccine an ideal blueprint for understanding how stable immunological memory develops.

The researchers studied more than 50 healthy adults who had just received a yellow fever vaccination and monitored their immune response over the course of a year. They also analysed blood samples from people who had been vaccinated against yellow fever between seven and 26 years earlier. This allowed them to directly compare the characteristics exhibited by the body's defence cells shortly after vaccination – and those they retain over the course of decades.

Powerful fighters, long-lasting guardians

The team focused their attention on what are known as T lymphocytes. There are many different types of these cells in the body, each specialising in a specific category of pathogens. Following a yellow fever infection (or a corresponding vaccination), those types of T cells that target body cells infected with the yellow fever virus proliferate preferentially. This rapidly creates a whole arsenal of suitable defence cells. Once they have successfully combated the virus, most of them die off. However, some 'memory cells' persist in the long term.

Right from the start of the immune response, not all T cells are dedicated to fighting the pathogen: some branch off to stand guard in the future – often for many decades.

"In the event of a repeat infection, they can then multiply very rapidly," explains Prof. Dr Kilian Schober, Heisenberg Professor of T-Cell Immunology at the Institute of Microbiology (Director: Prof. Dr Christian Bogdan) at Erlangen University Hospital, who led the study. "The immune system then reacts much more quickly than during the first encounter with the pathogen and can nip the infection in the bud." This induced immunological memory is also the main reason why vaccination protects against diseases.

Survival in energy-saving mode

But how exactly do these long-lived memory T cells differ from their counterparts that are active in fighting off infection? To answer this question, the researchers measured, amongst other things, the metabolic rate of the yellow fever-specific T cells. "We were thus able to show that some of them – namely those that later form the immunological memory – switch to a kind of energy-saving mode at an early stage," says Sina Frischholz from Schober's research group, who carried out the majority of the experimental work as part of her PhD. "They drastically slow down their metabolism and are thus able to survive for years and decades."

The team was surprised at how clearly this principle emerged. "The longest-lived immune cells are not the most active ones, but those that learn very early on to use their energy reserves sparingly," Frischholz emphasises. For the measurements, the team used, amongst others, a substance called puromycin. The more active a cell is, the more of it it incorporates into its proteins. By analysing this correlation, the researchers were able to determine how the metabolic activity of individual T cells was influenced by the yellow fever vaccination. "These data show very clearly that long-term immune memory is based on restraint, not on consistently high activity," explains Schober's colleague Dr Ev-Marie Schuster, who contributed her expertise in the field of cellular metabolism.

This pattern was already evident in the first few weeks following vaccination and was verified in participants whose vaccination had taken place many years earlier. The large volume and diversity of the measured data required complex computer-assisted analyses. "It was only through a systematic bioinformatic analysis that we were able to identify how stable this energy-saving programme remains over periods of decades," says Dr Myriam Grotz, who was responsible for the data analysis.

Observations also apply to the Covid vaccination

To ensure that this is a fundamental principle, the team tested its results in two different mouse models of bacterial and viral infections. The researchers also studied individuals who had just received a vaccination against SARS-CoV-2. The identified correlation was also reflected in these analyses. "This demonstrates that metabolic quiescence is not a special case specific to the yellow fever vaccine, but rather a fundamental principle of the immunobiology of memory cells," says Prof. Schober.

A consistently strong immune system is therefore not based on constant peak performance. "The key seems to be the ability of individual immune cells to shift down a gear at the right time, and precisely because of this, to remain operational for decades," emphasises Schober. "This changes our understanding of how long-lasting immunity develops – and could help us develop vaccines and immunotherapies in a more targeted way."



5,000-year-old bacteria defy 10 modern antibiotics

Ice cave bacteria could exacerbate the antibiotic resistance crisis – or help solve it.

Bacteria have evolved to adapt to all extreme conditions on Earth, from scorching heat to temperatures well below zero. Ice caves are just one of the environments that harbour a wide variety of microorganisms, representing a source of genetic diversity that has not yet been fully explored.

Romanian researchers have investigated the antibiotic resistance profiles of a bacterial strain that, until recently, was hidden in a 5,000-year-old layer of ice in an underground ice cave – and found that it could offer a way to develop new strategies to prevent the rise of antibiotic resistance and to study the natural development and spread of resistance. They reported their discovery in Frontiers in Microbiology.

"The bacterial strain *Psychrobacter* SC65A.3, which was isolated from the Scarisoara ice cave, is resistant to several modern antibiotics despite its ancient origins and carries over 100 resistance genes," said the author, Dr Cristina Purcarea, a senior researcher at the Institute of Biology in Bucharest, part of the Romanian Academy. "But it can also inhibit the growth of several important antibiotic-resistant 'superbugs' and exhibits key enzymatic activities with significant biotechnological potential."

Ancient resistance to modern drugs

Psychrobacter SC65A.3 is a strain of the genus *Psychrobacter*, which comprises bacteria adapted to cold environments. Some species can cause infections in humans or animals. *Psychrobacter* bacteria have biotechnological potential, but their antibiotic resistance profiles are largely unknown. "The study of microbes such as *Psychrobacter* SC65A.3, which were isolated from millennia-old cave ice deposits, shows how antibiotic resistance developed naturally in the environment long before modern antibiotics were used," said Purcarea.

The team drilled a 25-metre-long ice core from the area of the cave known as the Great Hall, which spans a period of 13,000 years. To avoid contamination, the ice fragments extracted from the core were stored in sterile bags and frozen on the return journey to the laboratory. There, the researchers isolated various bacterial strains and sequenced

their genomes to determine which genes enable the strain to survive at low temperatures and which confer antimicrobial resistance and activity.
They tested the SC65A strain's resistance to 28 antibiotics from ten classes that are routinely used to treat bacterial infections or are reserved for this purpose, including antibiotics previously found to harbour resistance genes or mutations that give them the ability to withstand the effects of medication.
This allowed them to test whether the predicted mechanisms lead to measurable resistance. "The 10 antibiotics we found resistance to are frequently used in clinical practice in oral and injectable treatments for a range of serious bacterial infections," said Purcarea. Diseases such as tuberculosis, colitis and urinary tract infections can be treated with some of the antibiotics against which the researchers detected resistance, including rifampicin, vancomycin and ciprofloxacin.
SC65A.3 is the first *Psychrobacter strain* in which resistance to certain antibiotics – including trimethoprim, clindamycin and metronidazole – has been detected. These antibiotics are used to treat urinary tract infections, as well as infections of the lungs, skin, blood and the reproductive system. The resistance profile of SC65A.3 suggests that strains capable of surviving in cold environments could act as reservoirs for resistance genes – specific DNA sequences that help them survive exposure to drugs.

Potential risks

Bacterial strains such as the one studied here hold both a threat and a promise. "If melting ice releases these microbes, these genes could spread to modern bacteria and exacerbate the global problem of antibiotic resistance," said Purcarea. "On the other hand, they produce unique enzymes and antimicrobial compounds that could inspire new antibiotics, industrial enzymes and other biotechnological innovations.
In the genome of *Psychrobacter* SC65A.3, the researchers found nearly 600 genes with unknown functions, suggesting a previously untapped source for the discovery of new biological mechanisms. Analysis of the genome also revealed 11 genes that are potentially capable of killing other bacteria, fungi and viruses, or halting their growth.
Such potential is becoming increasingly important in a world where antibiotic resistance is a growing problem. Drawing on ancient genomes and uncovering their potential highlights the important role that the natural environment has played in the spread and development of antibiotic resistance. "These ancient bacteria are indispensable to science and medicine," Purcarea concluded, "but careful handling and safety measures in the laboratory are essential to reduce the risk of uncontrolled spread."

A healthy diet in early life influences lifelong brain health

Gut bacteria and prebiotics from onions or garlic mitigate long-term brain changes caused by early poor nutrition.

Consuming unhealthy foods at a young age leaves lasting changes in the brain and in dietary patterns, but gut bacteria can help restore a healthy diet, according to new research by University College Cork (UCC).
A diet high in fat and sugar during the early years of life can cause long-lasting changes in the way the brain regulates eating, even after the unhealthy diet has been stopped and body weight has returned to normal, researchers at APC Microbiome, a leading research institute at UCC, have found.
Children today grow up in an environment saturated with high-fat and high-sugar foods that are readily available and heavily advertised. From birthday parties and school fetes to sporting events and even as rewards for good behaviour, these foods have become an everyday part of childhood experiences.
This new research highlights the long-term effects of this early exposure and demonstrates that frequent consumption of energy-dense, nutrient-poor foods during childhood can shape preferences and establish unhealthy eating habits that persist into adulthood.
The study, published in the journal *Nature Communications*, also shows that interventions targeting the microbiota – including a specific strain of beneficial gut bacteria (*Bifidobacterium longum* APC1472) or prebiotic fibres (fructo-oligosaccharides (FOS) and galacto-oligosaccharides (GOS), which occur naturally in foods such as onions, garlic, leeks, asparagus and bananas and are widely used in fortified foods and prebiotic dietary supplements), could help prevent these effects if administered throughout life.
The researchers found that a high-fat, high-sugar diet during early life led to persistent changes in eating behaviour in adulthood in a preclinical mouse model. These behavioural changes were linked to lasting disruptions in the hypothalamus, a key region of the brain involved in appetite control and energy balance.



What we eat early in life matters

"Our findings show that what we eat at a young age really does matter," said Dr Cristina Cuesta-Martí, the study's lead author. "Early dietary exposure can have hidden, long-term effects on eating behaviour that are not immediately apparent from weight alone."
The study showed that an unhealthy diet in early life disrupts the brain pathways responsible for eating habits, with the effects persisting into adulthood, suggesting an increased risk of obesity later in life.
Importantly, targeted manipulation of the gut microbiota was able to counteract these long-term diet-related effects. The putative probiotic strain *Bifidobacterium longum* APC1472 led to a marked improvement in dietary habits whilst causing only minor changes to the overall microbiome composition, suggesting a targeted mode of action. By comparison, the prebiotic combination (FOS+GOS) led to more extensive shifts in the gut microbiome.

Targeted modulation of the gut microbiota can mitigate long-term effects

Study lead Dr Harriet Schellekens added: "Our findings show that targeted modulation of the gut microbiota can mitigate the long-term effects of an unhealthy diet in early life on later eating behaviour. Supporting the gut microbiota from birth helps to maintain healthier eating habits later in life."
Professor John F. Cryan, Vice-President for Research and Innovation at UCC and a contributor to the study, said: "Studies such as this are an example of how basic research can lead to potential innovative solutions to major societal challenges. By demonstrating how nutrition in early childhood shapes the brain pathways involved in regulating food intake, this work opens up new possibilities for interventions based on the microbiota".

The UCC-led study was carried out in collaboration with colleagues from the University of Seville (Spain), the University of Gothenburg (Sweden) and the Teagasc Food Research Centre (Fermoy, Ireland), and was funded by Research Ireland, a postgraduate scholarship from the Irish Government and a research grant from the Biostime Institute for Nutrition & Care.