CENTER FOR NEUROSCIENCE
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UNIVERSITY OF COIMBRA
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University of Coimbra study reveals how Parkinson's disease can originate in the intestine

Scientists at the University of Coimbra (UC) reveal how Parkinson's disease can be triggered in the intestine and then progress to the brain. The results of the study have just been published in Gut, a leading international journal in the field of gastroenterology, and represent another key piece in the “puzzle” complex of what is the second most frequent neurodegenerative disease in the world and with a tendency to increase in the coming decades.

The study took place over the past five years at the Center for Neuroscience and Cell Biology (CNC-UC), and was funded by Santa Casa da Misericórdia de Lisboa (SCML) and by the Foundation for Science and Technology (FCT) in more than half a million euros.

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The team, led by Sandra Morais Cardoso, professor at the Faculty of Medicine of the University of Coimbra (FMUC), and Nuno Empadinhas, a researcher at the CNC-UC, studied, in mice, the effects of chronic ingestion of BMAA, a toxin produced by cyanobacteria and other microbes, and which can accumulate, for example, in some aquatic animals such as bivalves, shellfish and fish.

Building on previous studies that point to the existence of several "types" of Parkinson's disease, UC scientists demonstrate, for the first time, that chronic ingestion of this environmental microbial toxin eliminates very specific groups of bacteria that protect the intestinal mucosa and that regulate immunity at the level of this essential barrier. From here, a chain of events begins that spreads to a specific region of the brain, mainly damaging the mitochondria, organelles that, among other functions, act as energy factories for cells.

"**We have characterized the effects of this toxin, from the selective erosion of the intestinal microbiome to the alteration of immunity in the ileum (specific region of the intestine), to the specific degeneration of neurons that produce dopamine in the brain. Interestingly, the change in the intestinal barrier and immunity led to the classic brain marker of the disease appearing first in the intestine**", explains Sandra Morais Cardoso, clarifying that "**the propagation is slow and progressive and can occur through the blood or the vagus nerve (which connects the intestine to the brain), until it reaches the region of the brain associated with Parkinson's disease, where it affects the mitochondria of these neurons, which end up dying".**

Considering that the clinical diagnosis of Parkinson's disease only occurs when the first motor symptoms appear (tremors, muscle rigidity and slow movements), this study indicates that the disease may, in some cases, have appeared in the intestine many years earlier.

Sandra Morais Cardoso and Nuno Empadinhas explain that they decided to test this hypothesis, as "**many patients present intestinal symptoms several years before the clinical diagnosis and also because there seems to be a direct association between environmental toxicities and the onset of this disease described about 200 years ago, but whose origin is still unknown**". The results of the study now published "**do not represent a cure, but reinforce the possibility that there are cases of Parkinson's that appear first in the intestine. On the other hand, they confirm that a metabolite produced by certain bacteria can, inadvertently, trigger neurodegenerative processes specific to this disease**".

This investigation, they say, "**confirms that there is a direct communication between bacteria and mitochondria, that is, although this toxin is produced by some bacteria and attacks others that, in this case, are sentinels of immunity in the intestinal mucosa, it also attacks intestinal mitochondria and of the brain**". And they conclude, "**the toxin therefore has antibiotic action and will have originated in the wars between bacteria during the many millions of years of evolution, but unlike the antibiotics we use to fight bacteria that cause infections, it has a harmful side effect double: attacks beneficial bacteria and mitochondria**".

On the other hand, notes Nuno Empadinhas, this study alerts to a potential danger of chronic ingestion of BMAA in diets rich in aquatic foods, in which the levels of the toxin are unknown. It states that "**bioaccumulation of BMAA should be a concern**" and argues that, "**for the sake of food safety and public health, this specific toxin, which very rarely produces symptoms of acute intoxication, should be included in monitoring programs as it is confirmed that when consumed chronically, it can damage the intestinal microbiome and barrier, triggering disease**".

Asked if, and how, it is possible to block the circuit now shown, thus preventing the disease from spreading to the brain, Sandra Morais Cardoso and Nuno Empadinhas admit that yes,

but that it will be "**a multidisciplinary challenge that, in addition to identifying the molecular targets of the toxin and strategies to inactivate it, involves reestablishing and maintaining the community of protective bacteria, with the aim of strengthening and preserving the intestinal barrier**". It is noteworthy that, they conclude, "**if this strategy can be activated in the early stages of the disease (before the motor changes), it will be possible to prevent its progression**".

Cristina Pinto

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