New evidence suggests link between gut health and Parkinson's disease

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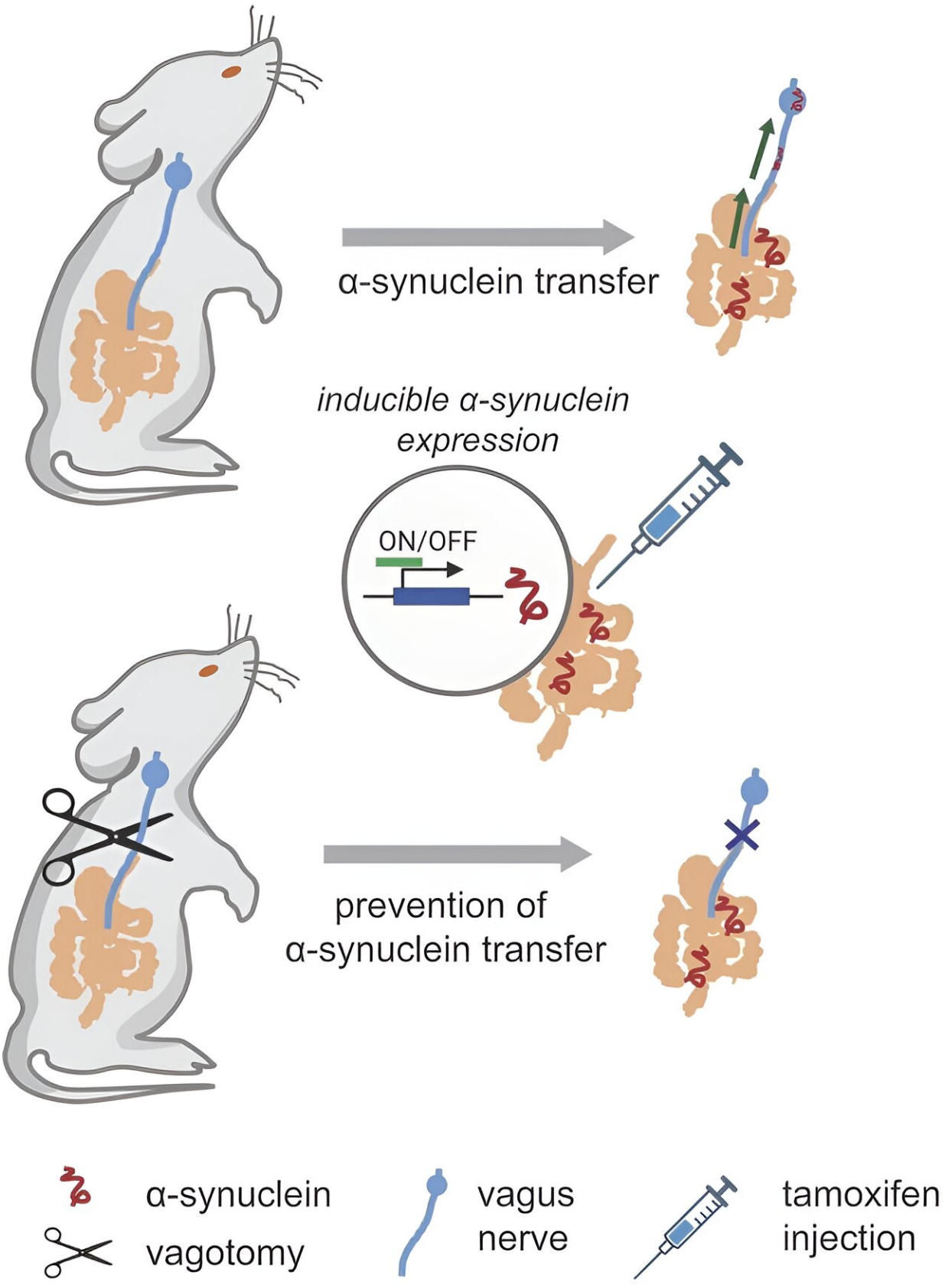
α-synuclein transfer
inducible α-synuclein expression
ON/OFF
prevention of α-synuclein transfer
α-synuclein
vagotomy
vagus nerve
tamoxifen injection

Credit: *JCI Insight* (2023). DOI: 10.1172/jci.insight.172192

While previous studies suggest Parkinson's disease begins in the gut and spreads to the brain, how the process occurs has been elusive. Now, a pre-clinical study led by Duke Health researchers provides new evidence that bolsters the gut-brain connection.

Reporting Dec. 8 in the journal *JCI Insight*, the team describe a process in which a protein found in the gut called alpha-synuclein (□-synuclein) travels through the nervous system and reaches susceptible nerves in the brain.

"It's when alpha-synuclein proteins become corrupted that this transport system becomes an issue," said senior author Rodger Liddle, M.D., professor in the Department of Medicine at Duke University School of Medicine. "If they are corrupted in the gut and are then able to spread to the brain, they could form clumps known as Lewy bodies, which are the hallmark of Parkinson's disease and other forms of dementia."

Parkinson's disease is a long-term degenerative disorder that impairs voluntary movement. It is estimated that up to 10 million people worldwide are living with the disease.

There is growing evidence that the gut plays a role in developing Parkinson's. One clue is that gastrointestinal symptoms such as constipation often happen before motor skills decline.

Liddle and colleagues focused on specialized cells that line the gut called enteroendocrine cells. These cells react to their environment and sense toxicants like herbicides and pesticides in the intestine; they also harbor

□-synuclein.

In experiments with cell cultures and mice, the researchers found that enteroendocrine cells transport □-synuclein from gut mucosal cells to the brainstem via the vagus nerve—the body's superhighway connecting the gut and brain.

"We hypothesize that something in the gut is corrupting □-synuclein, causing it to misfold," Liddle said. "Whether this is toxicants or some other exposure, we don't know. But we have demonstrated here that there is a route for pathologically misfolded □-synuclein to be transported from enteroendocrine cells to the brain, where they can aggregate to form Lewy body deposits."

Liddle said the research team was able to stem the spread of □-synuclein by severing the vagus nerve in the animals. The finding sets the foundation for designing therapies that could block the transport system or reset the altered gut-brain signaling.

More information: Rashmi Chandra et al, Gut mucosal cells transfer α-synuclein to the vagus nerve, *JCI Insight* (2023). DOI: 10.1172/jci.insight.172192

Provided by Duke University