Researchers overturn the theory of Parkinson's disease

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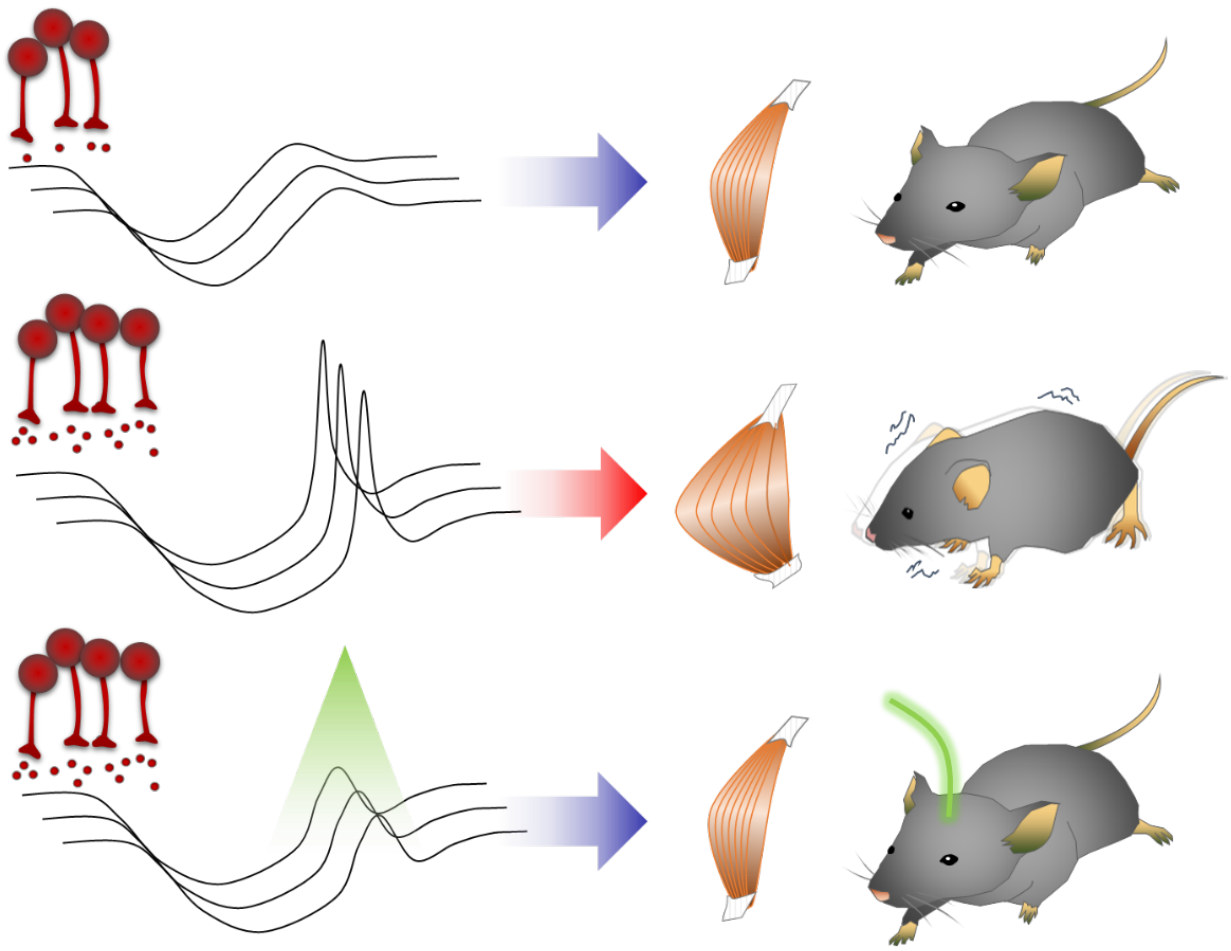

Inhibitory inputs from the basal ganglia inhibit thalamic neurons (upper). In low-dopamine states, like PD, rebound firing follows inhibition and causes movement disorders (middle). The inhibition of rebound firing alleviates PD-like symptoms in a mouse model of PD. Credit: KAIST

A KAIST research team has identified a new mechanism that causes the hallmark symptoms of Parkinson's disease, namely tremors, rigidity, and loss of voluntary movement.

The discovery, made in collaboration with Nanyang Technological University in Singapore, presents a new perspective to three decades of conventional wisdom in Parkinson's disease research. It also opens up new avenues that can help alleviate the motor problems suffered by patients of the disease, which reportedly number more than 10 million worldwide. The research was published in *Neuron* on August 30.

The research team was led by Professor Daesoo Kim from the Department of Biological Sciences at KAIST and Professor George Augustine from the Lee Kong Chian School of Medicine at NTU. Dr. Jeongjin Kim, a former postdoctoral fellow at KAIST who now works at the Korea Institute of Science and Technology (KIST), is the lead author.

It is known that Parkinson's disease is caused by a lack of dopamine, a chemical in the brain that transmits neural signals. However, it remains unknown how the disease causes the motor problems that plague Parkinson's disease patients.

Smooth, voluntary movements, such as reaching for a cup of coffee, are controlled by the basal ganglia, which issue instructions via neurons (nerve cells that process and transmit information in the brain) in the thalamus to the cortex. These instructions come in two types: one that triggers a response (excitatory signals) and the other that suppresses a response (inhibitory signals). Proper balance between the two controls movement.

A low level of dopamine causes the basal ganglia to severely inhibit target neurons in the thalamus, called an inhibition. Scientists have long

assumed that this stronger inhibition causes the motor problems of Parkinson's disease patients.

To test this assumption, the research team used optogenetic technology in an animal model to study the effects of this increased inhibition of the thalamus and ultimately movement. Optogenetics is the use of light to control the activity of specific types of neurons within the brain.

They found that when signals from the basal ganglia are more strongly activated by light, the target neurons in the thalamus paradoxically became hyperactive. Called rebound excitation, this hyperactivity produced abnormal muscular stiffness and tremor. Such motor problems are very similar to the symptoms of Parkinson's disease patients. When this hyperactivity of thalamic neurons is suppressed by light, mice show normal movments without Parkinson's disease symptoms. Reducing the levels of activity back to normal caused the motor symptoms to stop, proving that the hyperactivity caused the motor problems experienced by Parkinson's disease patients.

Professor Kim at KAIST said, "This study overturns three decades of consensus on the provenance of Parkinsonian symptoms." The lead author, Dr Jeongjin Kim said, "The therapeutic implications of this study for the treatment of Parkinsonian symptoms are profound. It may soon become possible to remedy movement disorders without using L-DOPA, a pre-cursor to dopamine."

Professor Augustine at NTU added, "Our findings are a breakthrough, both for understanding how the brain normally controls the movement of our body and how this control goes awry during Parkinson's disease and related dopamine-deficiency disorders."

The study took five years to complete, and includes researchers from the Department of Bio & Brain Engineering at KAIST.

The research team will move forward by investigating how hyperactivity in neurons in the thalamus leads to abnormal movement, as well as developing therapeutic strategies for the disease by targeting this neural mechanism.

More information: Jeongjin Kim et al, Inhibitory Basal Ganglia Inputs Induce Excitatory Motor Signals in the Thalamus, *Neuron* (2017). DOI: 10.1016/j.neuron.2017.08.028

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