Blocking key enzyme halts Parkinson's disease symptoms in mice

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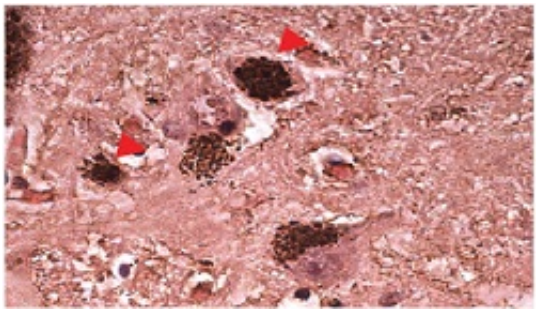

Clumps of the protein a-synuclein in a Parkinsonian brain. Credit: Donghoon Kim/Johns Hopkins Medicine

Researchers at Johns Hopkins say they have gleaned two important new clues in the fight against Parkinson's disease: that blocking an enzyme called c-Abl prevents the disease in specially bred mice, and that a chemical tag on a second protein may signal the disorder's presence and progression. Their work, described online June 27 in *The Journal of Clinical Investigation*, suggests both a promising target for drug research and a tool that could speed Parkinson's disease research more broadly, they say.

"There were indications that c-Abl activity leads to Parkinson's disease, and our experiments show there is indeed a connection," says Ted Dawson, M.D., Ph.D., professor of neurology and director of the Institute for Cell Engineering at the Johns Hopkins University School of Medicine. "There is already a Food and Drug Administration-approved c-Abl inhibiting drug in use for leukemia," he adds, "so we're interested in whether it could be used safely against Parkinson's disease or as a starting point to develop other treatments."

Autopsies have revealed that c-Abl is especially active in the brains of people with Parkinson's disease, a progressive disorder of the nervous system that affects movement. Additionally, studies in mice bred to be prone to the disease found drugs that block c-Abl may prevent or slow it. But, says Han Seok Ko, Ph.D., assistant professor of neurology at Johns Hopkins, "the drugs used in those studies could also have been blocking similar proteins, so it wasn't clear that blocking c-Abl was what benefited the animals by either preventing symptoms or influencing disease progression."

The researchers' new experiments started with mice genetically engineered to develop the disease and "knocked out" the gene for c-Abl, a move that reduced their disease symptoms. Conversely, genetically dialing up the amount of c-Abl the mice produced worsened symptoms and hastened the disease's progression. Increasing c-Abl production also caused normal mice to develop Parkinson's disease, the researchers say.

To learn more about how that happened, the team took a look at how c-Abl interacts with another protein, ?-synuclein. It's long been known that clumps of ?-synuclein in the brain are a hallmark of Parkinson's. The Johns Hopkins researchers found that c-Abl adds a molecule called a phosphate group to a specific place on ?-synuclein, and that increasing levels of c-Abl drove more ?-synuclein clumping along with worsening symptoms, says Dawson.

"We plan to look into whether ?-synuclein with a phosphate group on the spot c-Abl targets could serve as a measure of Parkinson's disease severity," he says. No such objective, biochemical measurement exists now, he notes, which hampers studies of potential therapies for the disease.

Dawson and Ko caution that the use of the anti-leukemia drug nilotinib is not yet indicated for Parkinson's disease patients and that further studies are needed before their results can be applied to clinical care.

About 60,000 Americans are diagnosed with

Parkinson's disease each year, and up to 10 million people worldwide are living with the disease, according to the Parkinson's Disease Foundation. People with the disease commonly experience tremors; slow, stiff movement; mood disorders; sleep disorders; and other symptoms. Certain gene variants and environmental exposures have been linked to Parkinson's disease, though its causes are still under investigation.

More information: Saurav Brahmachari et al, Activation of tyrosine kinase c-Abl contributes to ?-synuclein–induced neurodegeneration, *Journal of Clinical Investigation* (2016). DOI: 10.1172/JCI85456

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