Deterioration of brain cells in Parkinson's disease is slowed by blocking the Bach1 protein, preclinical study shows

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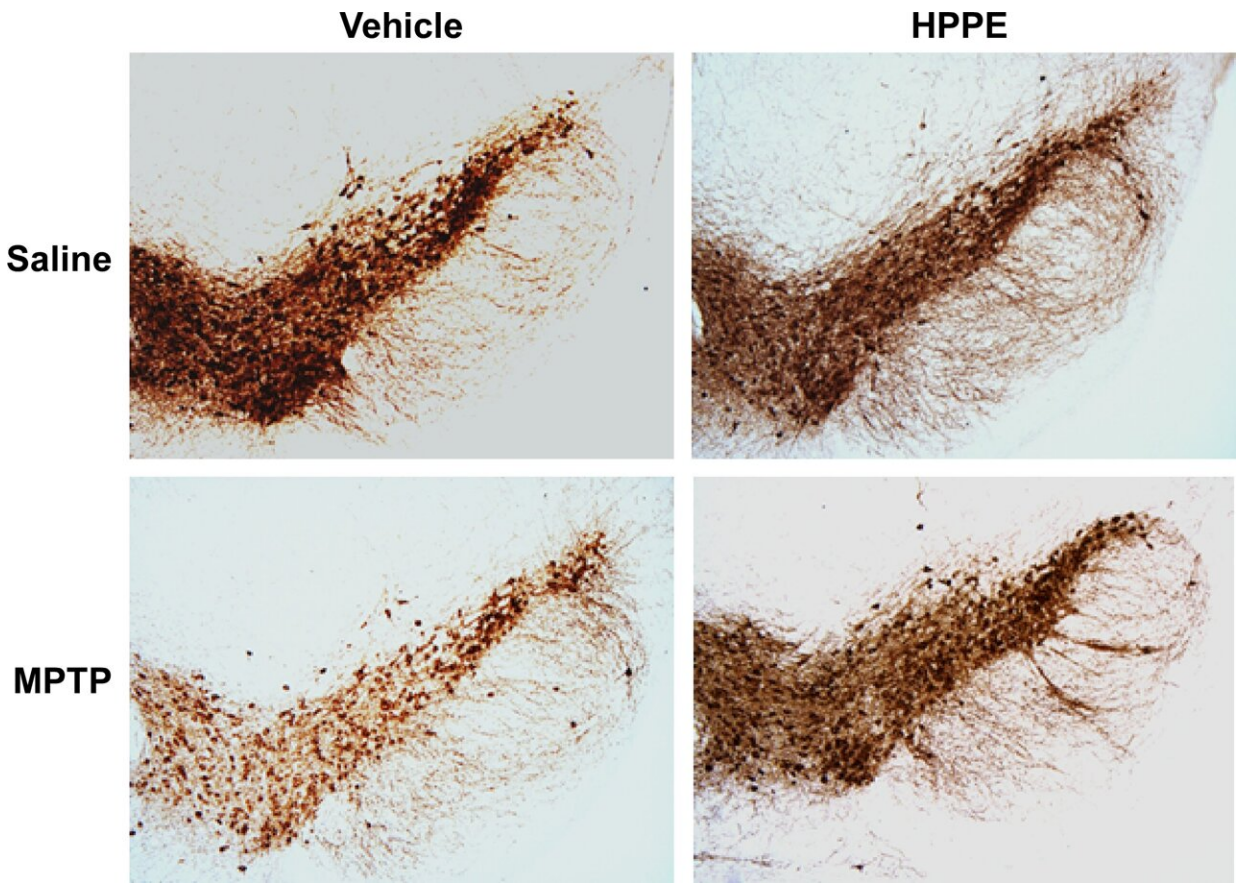

Dopamine producing brain cells (stained brown) were protected with HPPE (right panels) in neurotoxin-based PD model (MPTP; bottom) compared to vehicle control cells (left panels). Credit: Dr. Bobby Thomas from the Medical University of South Carolina.

Parkinson's disease (PD) is the most common neurodegenerative movement disorder, afflicting more than 10 million people worldwide and more than one million Americans. While there is no cure for PD, current therapies focus on treating motor symptoms and fail to reverse, or even address, the underlying neurological damage. In a new study, researchers at the Medical University of South Carolina (MUSC) have identified a novel role for the regulatory protein Bach1 in PD. Their results, published on Oct. 25 in the *Proceedings of the National Academy of Sciences*, showed that levels of Bach1 were increased in postmortem PD-affected brains, and that cells without Bach1 were protected from the damages that accumulate in PD. In collaboration with vTv Therapeutics, they identified a potent inhibitor of Bach1, called HPPE, that protected cells from inflammation and the buildup of toxic oxidative stress when administered either before or after the onset of disease symptoms.

"This is the first evidence that Bach1 is dysregulated in Parkinson's disease," said Bobby Thomas, Ph.D., professor of Pediatrics in the College of Medicine and the SmartState COEE Endowed Chair in Pediatric Neurotherapeutics.

In PD, brain cells that produce the chemical messenger dopamine begin to die as the disease progresses, resulting in tremors and other disruptions to motor function. Additionally, as we age, neurons accumulate damage through inflammation and the buildup of toxic oxidative stress.

There are many genes that combat these destructive pathways, many of which are controlled by two key proteins: Nrf2 and Bach1. Nrf2 functions to turn on the expression of over 250 genes that are involved in protecting the cell from these stressors. Conversely, Bach1 prevents these genes from being activated.

Thomas's lab found that levels of Bach1 are increased in autopsied brains of patients with PD, as well as toxin-based preclinical PD models, suggesting that high levels of Bach1 may contribute to PD pathophysiology. To confirm this, the researchers depleted Bach1 in a PD mouse model and showed that dopamine-producing neurons were protected from some of the destructive stress pathways.

To determine how the loss of Bach1 protected neurons from accumulated stress, they analyzed the entire genome of brains from Bach1-depleted mice and looked at which genes were activated.

"What we found was that Bach1 not only represses the expression of protective genes that are under the control of Nrf2, but it also regulates the expression of many other genes not directly regulated by Nrf2," said Thomas. "So there are additional advantages to inhibiting Bach1 besides just activating Nrf2. Ideally you would want a drug that inhibits Bach1 and also activates Nrf2."

To that end, Thomas partnered with the North Carolina-based company vTv Therapeutics to develop Bach1 inhibitors. Using its proprietary TTP Translational Technology platform, vTv discovered several potential candidates that were validated by Thomas. The top candidate, HPPE, functioned as a superior Bach1 inhibitor in in vitro models. Importantly, HPPE was also a potent activator of Nrf2.

Therefore, pharmacological intervention using HPPE provided the dual benefit of stabilizing Nrf2 and inhibiting Bach1. But how would HPPE work in a preclinical PD mouse model?

The effectiveness of HPPE was tested in a neurotoxin-based PD mouse model. HPPE alleviated toxin-induced PD symptoms when given either before the induction of disease or after the onset of disease symptoms. Further analyses showed that HPPE protects neurons from destructive

pathways by turning on antioxidant genes and turning off pro-inflammatory genes.

Interestingly, HPPE worked better at protecting neurons than current FDA-approved Nrf2 activators, such as Tecfidera (dimethyl fumarate). Current activators function as electrophiles—they permanently bind to and modify proteins, which can lead to cellular toxicity or activation of the immune system—and have many side effects.

"The most interesting aspect of the study is that the Bach1 inhibitor is a non-electrophile, so it doesn't work like the FDA-approved Nrf2 activators," said Thomas. "As a result of this difference, hopefully, HPPE will not demonstrate as many side effects."

Disruption of Bach1 and the simultaneous activation of Nrf2 clearly provide a strong basis for using HPPE as a potential therapeutic in PD. But several questions remain unanswered. While there were no side effects observed with acute treatment using HPPE in the PD mouse model, one key goal moving forward is to determine what impacts, if any, long-term use of HPPE might have. Another key question centers on the benefits of modulating this pathway in more chronic models of PD, other cell types in the brain and potentially other dementias.

"This pathway may be beneficial whenever you have impairments in anti-inflammatory pathways or mitochondrial dysfunctions," said Thomas. "I think any disease that has these kinds of etiologies would benefit from modulating this pathway."

More information: Bach1 derepression is neuroprotective in a mouse model of Parkinson's disease, *Proceedings of the National Academy of Sciences* (2021). DOI: 10.1073/pnas.2111643118.