New hope from old drugs in fight against Parkinson's (Update)

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Representative images illustrating TH+ neurons in the substantia nigra pars compacta (SNpc). MPTP treated animals show loss of TH+ neurons relative to control animals treated with saline or saline plus clenbuterol. Scale bar, 100 mm. Credit: S. Mittal et al., Science (2017)

Scientists have found early hints that compounds in certain asthma drugs might be able to combat Parkinson's disease.
The researchers cautioned that their findings are only a first step. Much more work is needed before they can lead to any new treatment for Parkinson's.

The compounds are known as beta-2 adrenergic agonists, and they are mainly found in drugs that treat asthma and certain other lung conditions by dilating the airways. They include medications such as albuterol (ProAir, Ventolin) and metaproterenol.

The new study, published Sept. 1 in *Science*, found that the compounds appear to dampen activity in a gene implicated in Parkinson's disease.

"We think this is an exciting potential pathway to developing new treatments for Parkinson's," said senior researcher Dr. Clemens Scherzer. He's a neurologist at Brigham and Women's Hospital and Harvard Medical School in Boston.

But he cautioned against jumping to conclusions. Doctors should not start prescribing asthma medications to their Parkinson's patients.

A researcher who wrote an editorial accompanying the study agreed.

"The big caution here is that these are FDA-approved medications, and doctors could prescribe them off-label," said Dr. Evan Snyder, a professor at Sanford Burnham Prebys Medical Discovery Institute in San Diego.

He was referring to the fact that doctors are allowed to prescribe drugs for reasons other than their officially approved uses.

"My worry is that people might take these drugs in an unregulated fashion," said Snyder.
That said, he called the new findings promising. "I think this is enough to justify moving toward properly done clinical trials," Snyder said.

Parkinson's is a movement disorder that affects nearly 1 million people in the United States alone, according to the Parkinson's Disease Foundation.

The root cause is unclear, but as the disease progresses, the brain loses cells that produce dopamine—a chemical that regulates movement. That results in symptoms such as tremors, stiff limbs, and balance and coordination problems that gradually worsen over time.

Many people with Parkinson's have a buildup of protein clumps, called Lewy bodies, in the brain. They mainly consist of a protein called alpha-synuclein.

Scientists aren't sure whether that protein buildup is actually a cause of Parkinson's or just "collateral damage" from the disease process, Snyder said.

But, he added, mutations in the alpha-synuclein gene have been implicated as one cause of rare, inherited cases of Parkinson's.

According to Scherzer, there's also evidence that "risk variants" of the alpha-synuclein gene can contribute to more common forms of Parkinson's.

Researchers are already trying to develop drugs that target alpha-synuclein—by clearing it from the brain, for example. Scherzer said his team took a different approach.

"We thought the best way to tackle this might be to 'turn down' the production of alpha-synuclein," he explained.
So the researchers screened more than 1,100 compounds—from prescription drugs to vitamins and herbs—to find any that curbed activity in the alpha-synuclein gene.

Beta-2 agonists turned out to be a winner.

Next, the researchers turned to a Norwegian database that tracks all drug prescriptions in that country. Out of more than 4 million people, Scherzer's team identified 600,000-plus who'd used the asthma drug salbutamol (called albuterol in the United States).

Overall, those people were one-third less likely to develop Parkinson's over 11 years, versus non-users. In contrast, Parkinson's risk was doubled among people who'd ever used the blood pressure drug propranolol (Inderal).

Propranolol is a beta-blocker—a class of medications normally used to treat blood pressure and heart disease. The researchers found that beta-blockers may actually increase activity in the alpha-synuclein gene, Scherzer said.

However, he stressed, the findings do not prove that asthma drugs prevent Parkinson's—or that beta-blockers contribute to it.

"You need a clinical trial to prove cause-and-effect," Scherzer said.

He did, however, caution on rushing to a clinical trial. To Scherzer, it would be wise to try to refine the beta-2 agonist compounds, to make them more effective at dialing down alpha-synuclein.

He also said any future studies could focus on Parkinson's patients who carry variants of the alpha-synuclein gene that have been tied to the disease.
Snyder agreed that any effects of beta-2 agonists might vary based on individuals' genetics.

The findings raise another, more immediate question: What about Parkinson's patients who are on beta-blockers—the drugs linked to a higher risk of the disease?

Both Snyder and Scherzer stressed that they should not abandon any medications they need for high blood pressure or heart disease.

But, Scherzer said, patients who are concerned could ask their doctor whether there are any alternative medications.

**More information:** S. Mittal el al., "ß2-Adrenoreceptor is a regulator of the α-synuclein gene driving risk of Parkinson's disease," *Science* (2017). [science.sciencemag.org/cgi/doi ... 1126/science.aaf3934](science.sciencemag.org/cgi/doi ... 1126/science.aaf3934)

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