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PARKINSON DISEASE

Asthma drug could protect against PD

> This research is an exciting first step

An existing asthma medication could be repurposed as a therapy for Parkinson disease (PD), according to a new study. Researchers found that salbutamol, a β2-adrenoreceptor (β2AR) agonist that is used to treat asthma, was associated with a reduced risk of PD in a Norwegian population. This treatment might act through epigenetic suppression of *SNCA*, the gene that encodes α-synuclein (α-syn).

Aggregates of α-syn in the brain are a key hallmark of PD. Duplication or triplication of *SNCA*, which results in increased levels of α-syn, is known to cause familial PD, and more-modest increases in α-syn have been suggested to contribute to sporadic forms of the disease. Therapies have been tested that attempt to clear existing α-syn or block its conversion into a toxic form, but have thus far shown little success.

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"We hypothesized that the most direct and acute solution would address the problem at its origin and simply turn down excessive *SNCA* transcription," comments corresponding author Clemens Scherzer. To this end, the team carried out a screen on 1,126 compounds to identify modifiers of *SNCA* expression in a human neuroblastoma cell line. Four compounds significantly reduced levels of α-syn, three of which were β2AR agonists.

To further characterize the effects of β2AR activation, Scherzer and colleagues treated wild-type mice with the β2AR agonist clenbuterol, which crossed the blood–brain barrier and reduced the levels of α-syn in the midbrain and substantia nigra. Conversely, α-syn levels were significantly increased in neurons from mice harbouring a deletion of *Adarb2*, which encodes β2AR. Interestingly, the researchers found that clenbuterol treatment reduced histone acetylation at the promoter and enhancer regions of the human *SNCA* gene, suggesting that β2AR stimulation inhibits *SNCA* expression via an epigenetic mechanism.

The team then investigated the effects of β2AR modulation in humans by examining the Norwegian Prescription Database, which contains information on all drugs prescribed by the country's public health system since 2004. In this population, treatment with salbutamol correlated with a decreased risk of PD (risk ratio (RR) 0.66). By contrast, treatment with propranolol, a β2AR antagonist prescribed for cardiovascular diseases, correlated with an increased risk of PD (RR 2.20).

Finally, the investigators tested whether β2AR agonism also exerted a protective effect in experimental models of PD. The team observed that clenbuterol treatment protected against neuronal degeneration in the substantia nigra in a mouse model of PD, and also increased viability in induced pluripotent stem cells derived from patients with an *SNCA* triplication.

"This research is an exciting first step," comments Scherzer. "Much work remains to be done, and difficult questions need be addressed on the way to a smart clinical trial."

The team are looking to lay the foundations for such a trial by further characterizing the pathways that link β2AR with PD pathobiology, and conducting epidemiological studies in additional populations. "It is important to carefully try to solve some of these questions in a thoughtful and deliberate manner — hopefully ultimately setting the stage for a trial that is poised for success," concludes Scherzer.

Charlotte Ridler

ORIGINAL ARTICLE Mittal, S. *et al.* α2-Adrenoreceptor is a regulator of the α-synuclein gene driving risk of Parkinson's disease. *Science* **357**, 891–898 (2017)