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Identification of new α -synuclein regulator by non-traditional drug development pipeline

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Parkinson's disease (PD) is pathologically characterized by the loss of dopaminergic neurons in the substantia nigra and by abnormal accumulation of α -synuclein protein fibrils in the form of Lewy bodies. These aggregated proteins result in progressive cytotoxic changes, including disruption of ER-Golgi trafficking, dysfunction of mitochondria, and impairment of lysosome. Human genetic studies have shown that duplication or triplication of the α -synuclein gene (SNCA) causes early-onset, familial PD that typically progresses to Parkinson's disease dementia.^{1, 2} SNCA mRNA and protein levels in these patients are increased by 50 to 100%.³ Thus, a pharmacologic reduction of α -synuclein could offer a new avenue for treating PD.

Using a screen of FDA-approved drugs and natural compounds, Mittal and colleagues recently reported that modulation of the β 2-adrenoreceptor regulates SNCA expression.⁴ Treatment with selective β 2-adrenoreceptor agonists (metaproterenol, clenbuterol, salbutamol) significantly reduced SNCA expression in rat primary cortical neurons. Conversely, treatment of SK-N-MC cells with the β -blocker propranolol increased SNCA mRNA and protein levels, indicating a bidirectional regulation of SNCA expression that is mediated by the β 2-adrenoreceptor. Additional experiments in the MPTP-induced PD mouse model and an iPSC-derived neuronal culture from a PD patient with SNCA locus triplication demonstrated the same directionality of effects: clenbuterol treatment protected MPTP-treated mice from nigral degeneration, and clenbuterol-treated neuronal iPSCs had significantly decreased SNCA mRNA and protein levels compared to untreated cells. Integrative genomic analysis found that the β 2-adrenoreceptor mediates its expression control through H3K27 histone acetylation at the SNCA promoter and enhancer regions.

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Hot topic commentary on: Mittal S, Bjornevik K, Im DS, et al. β 2-Adrenoreceptor is regulator of the α -synuclein gene driving risk of Parkinson's disease. *Science* 2017;357:891–898.

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Next, Mittal et al. evaluated the risk of PD in individuals exposed to either salbutamol or propranolol in population-based health registry data from Norway. Their analysis suggested that treatment with salbutamol is associated with decreased risk of PD, while propranolol increases the risk. However, due to the small number of treated PD cases and lack of correction for possible confounders, the reported association results should be interpreted with caution and need confirmation in independent epidemiologic studies prior to application in the clinical setting. In particular, it is premature to advise any medication changes based on these initial findings.

Taken together, these results are noteworthy as they suggest that β 2-adrenoreceptor agonists could reduce risk for PD and act as disease-modifiers. The drug screening pipeline described in this paper could also be applied to other brain diseases that are caused by toxic gene dosage effects. This work highlights an avenue for repurposing existing drugs for alternative indications.

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