Breathing new life into an old target: pulmonary disease drugs for Parkinson’s disease therapy

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Abstract
Increases in α-synuclein protein expression are suspected to increase the risk of the development of Parkinson’s disease (PD). A recent study has demonstrated that β2-adrenergic receptor (β2AR) agonists decrease histone acetylation in the α-synuclein gene and suppress transcription. Coupled with the anti-inflammatory effects that are associated with β2AR activation, this two-pronged attack holds promise for PD treatment and the development of new therapeutic approaches for this disease.

Keywords: Epigenetic modification, Histone acetylation, Lewy body disease, Neuroinflammation, Neuroprotection, Parkinson’s disease, SNCA

Parkinson’s disease and the role of α-synuclein
Human genetic studies have shown that increases in the expression of SNCA, the gene encoding the α-synuclein protein, may increase the risk of the development of Parkinson’s disease (PD). In rare familial PD cases, copy number variants that result in multiplications of the SNCA gene cause an aggressive early-onset PD phenotype [1]. In idiopathic PD cases that lack mutations in the SNCA gene, genome-wide association studies have identified PD-associated promoter variants and variants in the 5’ and 3’ untranslated regions (UTRs) that may lead to increased SNCA expression [2]. The α-synuclein protein forms inclusions known as Lewy bodies and neurites that spread throughout much of the brain in PD-affected individuals. Intense research efforts have focused either on strategies to reduce the propensity of α-synuclein to aggregate, or on reducing the expression of α-synuclein. Here, we consider the genetic and epigenetic mechanisms that are involved in α-synuclein gene regulation and how these might inform future PD interventions.

Identification of a new target in Parkinson’s disease
In a recent study, Mittal et al. provided evidence that β2-adrenergic receptor (β2AR) agonists, which are the most common medications used for respiratory diseases, are associated with reduced PD risk in the Norwegian population [3]. Drugs that activate β2ARs (agonists) mimic the effects of endogenous catecholamines, including norepinephrine, epinephrine, and dopamine, and have effects on smooth muscle. β2AR agonists dilate bronchial passages and are used in asthma treatment and can relax uterine muscles and so are used in treating preterm labor. β2AR blockers, such as propranolol, antagonize epinephrine and norepinephrine and have broad utility in treating cardiovascular disease. In general, both β2AR blockers and long-acting agonists, as well as some short-acting agonists, penetrate the blood–brain barrier. In the study by Mittal et al., β2AR agonists were found to decrease SNCA expression in neurons in different experimental models. In defining the underlying mechanism, the authors showed that β2AR blockers increased, whereas agonists decreased, histone 3 lysine 27 acetylation in the α-synuclein promoter. Epigenetic mechanisms such as histone acetylation at the SNCA promoter have been shown to regulate gene expression by loosening chromatin and by improving the accessibility of chromatin for transcription factor binding [4]. SNCA mRNA levels could be reduced by an impressive ~ 30% in neurons exposed to salbutamol (also known as albuterol), metaproterenol, and clenbuterol, which are all β2AR agonists commonly used for the treatment of asthma. Based on the genetic risk imposed by increases in α-synuclein expression, a sustained 30%
Another remarkable observation from Mittal et al. was

Lessons learned from epidemiological studies

A high degree of overlap in the expression profiles in cells and tissues between β2AR and α-synuclein might provide confidence that this axis can be broadly targeted to decrease transcription factor binding in the SNCA promoter and thus the corresponding gene transcription. Surveys of carefully curated expression databases of human cells and tissues have revealed a wide distribution of β2AR in the body with notably high expression in immune cells [5]. By contrast, α-synuclein is primarily expressed in the brain, and a recent study using advanced genetic-sorting technology to isolate different mouse brain cell types for deep mRNA sequencing showed little or no expression of the β2AR gene (ADBR2) in cortical neurons compared with very high expression in microglial and endothelial populations that lacked SNCA [6].

The very high β2AR expression in microglia has not previously gone unnoticed, and β2AR agonists have demonstrated some efficacy in reducing neuroinflammation and neurodegeneration in multiple models of neurodegeneration [5]. Therefore, Mittal et al. have identified an exciting second purpose for β2AR agonists in reducing SNCA expression in some neurons, presumably those that express β2AR. Importantly, α-synuclein protein strongly activates pro-inflammatory responses in the brain. Therefore, the two expected therapeutic activities associated with β2AR agonists are not mutually exclusive. Even if β2AR agonists fail to act on SNCA in some neurons due to a lack of β2AR expression, there may still be therapeutic gain through a broad dampening of microglial activation caused by abnormal α-synuclein expression.

Challenges with translating existing drugs to the clinic

Mittal et al. used intraperitoneal injection of US Food and Drug Administration (FDA)-approved agonists to demonstrate efficacy in blocking SNCA promoter acetylation and in reducing SNCA expression in the mouse brain. In pre-clinical studies, β2AR agonists have demonstrated efficacy in reducing inflammation and neurodegeneration in cerebral ischemia, traumatic brain injury, and even in tau pathology models, but their positive effects required pretreatment [5]. Epidemiological studies will be needed to clarify the timing of agonist exposure relative to PD diagnosis. Furthermore, pre-clinical studies should evaluate whether treatment paradigms, rather than prevention (pretreatment) paradigms, have effects in models that rely on endogenous α-synuclein for neurodegeneration. Fortunately, such models are now in use in the PD research field [8].

Currently no β2AR agonists have been specifically developed for PD. Repurposing existing drugs may involve compromises in brain penetration, oral availability, half-life, specificity, and safety in elderly populations. However, there is a time delay and resource drain associated with de novo efforts to develop optimized new molecules. The early failure of a less-than-optimal β2AR agonist in efficacy trials may have an industry-wide effect by leading to the discontinuation of programs that aim to bring superior molecules to trial. Regrettably, in
PD clinical research, most efficacy trials have ended without any measurable end point due to a lack of knowledge of whether the drug had successfully engaged the desired target or produced the intended effect. When considering data from Mittal et al. and others, there is a clear mechanism of action in the reduction of α-synuclein levels and the possible reduction of neuroinflammation. These effects can be monitored in clinical trials using biomarkers and imaging approaches and incorporated early into rationally conceived development pipelines. One challenge is that α-synuclein levels in cerebral spinal fluid are already suppressed in PD populations [9], potentially reflecting compensatory changes, so early clinical studies should determine whether further reductions in α-synuclein levels are possible. The findings of Mittal et al. breathe new life into an old target and provide hope that disease modification in PD will be possible in the near future.

Abbreviations
PD: Parkinson’s disease; SNCA: Alpha-synuclein; β2AR: β2-adrenergic receptor

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Competing interests
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