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Gardenin A decreases neuroinflammation, activates antioxidant response and improves cognitive and motor function in A53T alpha synuclein overexpressing mice

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Abstract

Background:

Oxidative stress and neuroinflammation are widespread in the Parkinson's disease (PD) brain and contribute to the synaptic degradation and dopaminergic cell loss that result in cognitive impairment and motor dysfunction. The compound Gardenin A (GA) has been shown to activate the NRF2-regulated antioxidant pathway and inhibit the NFkB-regulated pro-inflammatory pathway in a *Drosophila* model of PD. Here, we evaluate the effects of GA on A53T alpha-synuclein overexpressing (A53TSyn) mice.

Methods:

A53TSyn mice were treated orally for 4 weeks with 0, 25, or 100 mg/kg GA. In the fourth week, mice underwent behavioral testing and tissue was harvested for immunohistochemical analysis of tyrosine hydroxylase (TH) and phosphorylated alpha synuclein (pSyn) expression, and quantification of synaptic, antioxidant and inflammatory gene expression. Results were compared to vehicle-treated C57BL6 mice.

Results:

Treatment with 100mg/kg GA improved associative memory and decreased abnormalities in mobility and gait in A53TSyn mice. GA treatment also reduced cortical and hippocampal levels of pSyn and attenuated the reduction in TH expression in the striatum. Additionally, GA increased cortical expression of NRF2 regulated antioxidant genes and decreased expression of NFkB regulated pro-inflammatory genes. GA was also readily detectable in the brains of treated mice.

Conclusions:

GA significantly improved cognitive deficits and motor dysfunction, and attenuated several pathological features in the brains of alpha-synuclein overexpressing mice. While these results are promising, future studies are needed to confirm these effects in other PD models, optimizing dosing and to more fully elucidate the mechanism of action of GA.