

## **THE CHOLESTEROL OXIDATION PRODUCTS MAY UNDERLIE A-SYNUCLEIN ACCUMULATION IN ALZHEIMER'S DISEASE AND PARKINSON'S DISEASE**

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Accumulation of  $\alpha$ -synuclein ( $\alpha$ -Syn) is a common hallmark of a group of brain disorders collectively known as synucleinopathies. These disorders include Parkinson's disease (PD), the most common movement disorder; dementia with Lewy bodies (DLB), the second most common form of dementia; multiple system atrophy (MSA), a neurodegenerative disease leading to severe physical impairment; and Alzheimer's disease (AD), the most common form of dementia. The role of  $\alpha$ -Syn in the pathogenesis of synucleinopathies is not understood, but experimental studies point to a potential neurotoxic role of high levels of this protein in its soluble or aggregated forms. We found that the oxysterol 27-hydroxycholesterol (27-OHC), the major cholesterol oxidation metabolite in human plasma, causes both AD-like pathology and PD-like pathology in human neuroblastoma cells and in organotypic slices. We found that 27-OHC increases  $\alpha$ -Syn transcription through activation of liver X receptors (LXR). Furthermore, we demonstrate that while activation of LXR with specific agonists increases, inhibition of LXR with specific antagonists reduces  $\alpha$ -Syn accumulation. Such results suggest a possible role of oxysterols and LXR signaling in synucleinopathies. Oxysterol levels are elevated in the circulation in hypercholesterolemic individuals. Interestingly, oxidative stress can also increase conversion of cholesterol to oxysterols. Our data are significant to identifying factors that may contribute to the pathogenesis of synucleinopathies and to the underlying cellular mechanisms. Identification of such factors and signaling pathways is paramount to understanding the pathophysiology of synucleinopathies including AD and