The cholesterol oxidation derivative 27 hydroxycholesterol regulates α-synuclein transcription-implications in synucleinopathies

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Accumulation of α-synuclein protein is a common hallmark of a group of brain disorders collectively known as synucleinopathies. These disorders include Parkinson's disease, dementia with Lewy bodies, multiple system atrophy and Alzheimer's disease. The causes of synucleinopathies are likely multi-factorial with several factors including genetic susceptibility and environmental agents, potentially participating in the pathogenesis of these diseases. 27-hydroxycholesterol (27-OHC) is an oxysterol produced from oxidation of cholesterol by the mitochondrial enzyme CYP 27A1. Cholesterol oxidation to 27-OHC is accelerated not only by diets rich in cholesterol but also by oxidative stress and aging. When formed in excess, 27-OHC has the ability to cross lipophilic membranes of the blood brain barrier and migrate into the brain where it can increase α-synuclein levels through over-activation of its cognate receptor, liver X receptor (LXR). We have incubated human neuroblastoma (SHSY5Y) cells, mouse dopaminergic neurons differentiated from embryonic stem cells, and human dopaminergic neurons differentiated from human normal dopaminergic neuronal precursor cells with 27-OHC and examined the effects of increased 27-OHC on the expression levels of α-synuclein. Our results show that 27-OHC dose-dependently increases the transcription of α-synuclein through modulation of LXR in the three different cell types. Identification of the oxysterol 27-OHC and the LXR as the underlying cellular mechanisms by which 27-OHC increases α-synuclein levels may help in designing therapeutic agents that can prevent, reverse, or stop the over-production of α-synuclein and ultimately may protect against *synucleinopathies.*