27-hydroxycholesterol increases α-synuclein protein levels through proteasomal inhibition in human dopaminergic neurons

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Accumulation of the α-synuclein (α-syn) protein is a hallmark of a group of brain disorders collectively known as synucleinopathies. The mechanisms responsible for α-syn accumulation are not well understood. Several studies suggest a link between synucleinopathies and the cholesterol metabolite 27-hydroxycholesterol (27-OHC). 27-OHC is the major cholesterol metabolite in the blood that crosses the blood brain barrier, and its levels can increase following hypercholesterolemia, aging, and oxidative stress, which are all factors for increased synucleinopathy risk. In this study, we determined the extent to which 27-OHC regulates α-syn levels in human dopaminergic neurons, the cell type in which α-syn accumulates in PD, a major synucleinopathy disorder. Our results show that 27-OHC significantly increases the protein levels, not the mRNA expression of α-syn. The effects of 27-OHC appear to be independent of an action through liver X receptors (LXR), its cognate receptors, as the LXR agonist, GW3965, or the LXR antagonist ECHS did not affect α-syn protein or mRNA levels. Furthermore, our data strongly suggest that the 27-OHC-induced increase in α-syn protein levels emanates from inhibition of the proteasomal degradation of this protein and a decrease in the heat shock protein 70 (HSP70). Identifying 27-OHC as a factor that can increase α-syn levels and the inhibition of the proteasomal function and reduction in HSP70 levels as potential cellular mechanisms involved in regulation of α-syn. This may help in targeting the correct degradation of α-syn as a potential avenue to preclude α-syn accumulation.