A-SYNUCLEIN NUROPATHOLOGY IN CONTROLLED BY NUCLEAR RECEPTORS AND ENHANCED BY DIETARY DOCOSAHEXAENOIC ACID IN A MOUSE MODEL OF PARKINSON'S DISEASE

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a-synuclein is a neuronal protein that accumulates progressively in Parkinson's disease and related synucleinopathies. a-synuclein normally interacts with membrane lipids, and oligomerization of a-synuclein in cultured cells is enhanced by polyunsaturated fatty acids (PUFA). We studied the effects of dietary changes in docosahexaenoic acid (DHA, 22:6) on a-synuclein cytopathology in mice transgenic for the Parkinson's disease-causing A53T mutation in human a-synuclein. A diet enriched in docosahexaenoic acid increased the accumulation of soluble and insoluble neuronal a-synuclein, neuritic injury and astrocytosis. Conversely, abnormal accumulations of a-synuclein and its deleterious effects were significantly attenuated by low dietary docosahexaenoic acid levels. Further results indicated a role for retinoic X receptor (RXR) and peroxisome proliferator-activated receptor g2 (PPARγ2) in a-synuclein oligomerization and suggested that docosahexaenoic acid may enhance a-synuclein oligomerization by acting as an activating ligand for these transcription factors. Our results provide in-vivo evidence of a deleterious effect for elevated brain polyunsaturated fatty acids levels on a-synuclein's neuropathology.