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Title: Alpha-synuclein, epigenetics, mitochondria, metabolism, calcium traffic, and circadian dysfunction in Parkinson's disease. An integrated strategy for management.

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Highlights:

- **Evidence for dysfunctional gene signals and their effects in sporadic Parkinson's disease is reviewed.**
- **An associated network of mitochondrial, metabolic, circadian and calcium signal abnormalities is analysed.**
- **A combination of physiological nutrients is proposed as a means to slow disease progression and the accumulation of pathogenic forms of alpha-synuclein.**

ABSTRACT

The motor deficits which characterise the sporadic form of Parkinson's disease arise from age-related loss of a subset of dopamine neurons in the substantia nigra. Although motor symptoms respond to dopamine replacement therapies, the underlying disease process remains. This review details some features of the progressive molecular pathology and proposes deployment of a combination of nutrients: R-lipoic acid, acetyl-L-carnitine, ubiquinol, melatonin (or receptor agonists) and vitamin D3, with the collective potential to slow progression of these features. The main nutrient targets include impaired mitochondria and the associated oxidative/nitrosative stress, calcium stress and impaired gene transcription induced by pathogenic forms of alpha-synuclein. Benefits may be achieved via nutrient influence on epigenetic signaling pathways governing transcription factors for mitochondrial biogenesis, antioxidant defences and the autophagy-lysosomal pathway, via regulation of the metabolic energy sensor AMP activated protein kinase (AMPK)