Title: Short chain fatty acid combination treatment protects against 6-OHDA and WT α-synuclein induced decreases in neurite growth in *in vitro* models of Parkinson's disease.

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Background: Parkinson's disease (PD) is a neurodegenerative disorder characterized by dopaminergic neuron degeneration. This degeneration is partly driven by over expression of α-synuclein (α-syn) and development of α-syn aggregates known as Lewy bodies throughout the substantia nigra. As well as motor dysfunction, PD presents with several chronic gastrointestinal comorbidities, which cause a decline of gut microbial diversity and microbially derived short chain fatty acids (SCFAs). Recent *in vivo* studies have shown SCFAs to be neuroprotective in various degenerative disease states, suggesting that SCFAs may protect against dopaminergic degeneration.

Methods: Human neuroblastoma SH-SY5Y cells were used as a model of human dopaminergic neurons, to examine the effects of SCFAs on neurite growth as a single cell readout of neuroprotective efficacy, in the presence and absence of the dopaminergic neurotoxin, 6-hydroxydopamine (6-OHDA) as an *in vitro* model of PD. Furthermore, we examined the effects of a SCFA combination treatment in SH-SY5Y cells transfected to overexpress wild type a-syn (WT α-syn) as a secondary model of PD related degeneration.

Results*:* Concurrent sodium acetate (NaOAc) treatment(25μM-200uM) for 72h, promoted neurite outgrowth in a concentration dependent manner. However, treatment with 50μM NaOAc didn't protect against neurite retraction induced by 10μM 6-OHDAtreatment for 72h. Conversely, a SCFA combination of 50μM NaOAc, 50μM Sodium Butyrate and 50μM Sodium Propionate did protect against 6-OHDA-induced decreases in neurite growth at 72h. Similarly, the transfected model of SH-SY5Y cells showed that this concurrent SCFA combination treatment at 50μM protected against WT α-syn associated neurite retraction at the 72h timepoint.

Conclusions: These findings provide proof-of-principle that SCFAs may protect against degeneration induced by a neurotoxin and a-syn overexpression in the SH-SY5Y cell line *in vitro*. This rationalizes the further study of SCFAs and SCFA producing microbes as potential neuroprotective therapies for PD.