Title: Short chain fatty acid combination treatment protects against 6-OHDA induced decrease in neurite growth in an in vitro model of Parkinson's disease.

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Background: Parkinson's disease (PD) is a neurodegenerative disorder characterized by dopaminergic neuron degeneration. This leads to motor dysfunction which is accompanied by gastrointestinal comorbidities such as constipation and gastroparesis. This results in a decline of gut microbial diversity and microbially-derived short chain fatty acids (SCFA). Recent *in vivo* studies have shown SCFAs to be anti-inflammatory and neuroprotective in various disease states. This suggests that SCFAs may protect against dopaminergic degeneration.

Methods: To test this hypothesis, this study utilized human neuroblastoma SH-SY5Y cells 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 well-established dopaminergic neurotoxin, 6-hydroxydopamine (6-OHDA) as an *in vitro* model of PD. 6-OHDA is selectively neurotoxic for dopamine neurons and induces mitochondrial dysfunction and oxidative stress thereby mimicking the characteristic cellular pathology seen in PD.

Results*:* Treatment with 25-200μM sodium acetate (NaOAc) for 72h, promoted neurite outgrowth in a concentration dependent manner. However, treatment with 50μM NaOAc did not protect against neurite retraction induced by treatment with 10μM 6-OHDA for 72h. In contrast, a combination of SCFAs of 50μM NaOAc, 50μM Sodium Butyrate (NaBu) and 50μM Sodium Propionate (NaPro) did protect against 6-OHDA-induced decreases in neurite growth at 72h.

Conclusions: Our findings provide proof-of-principle that combinations of SCFAs may protect against degeneration induced by a neurotoxin in a human dopaminergic cell line *in vitro*. This rationalizes the further study of SCFAs as potential neuroprotective therapies for PD.