Targeting the gut to protect from ascending pathology in the paraquat and lectin model of Parkinson's disease

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Background: Epidemiologic studies have shown that a commonly used pesticide, paraquat, has been linked to the development of Parkinson's Disease (PD)(1). Lectins are ubiquitous in the human diet and when uncooked, have the ability to enhance the toxicity of pesticides such as paraquat(2,3). A rat model of PD using oral administration of subthreshold doses of paraquat and lectin (P+L) has shown the pathology is mediated via the monosynaptic dopaminergic nigrovagal pathway(4). In the disease state, α-synuclein phosphorylated at the Ser129 site travels retrogradely from the gut via the vagus nerve to reach the Substantia nigra (SN), leading to dopaminergic neuron death and coinciding behavioral motor deficits in rats(4). A synthetic biosalt, squalamine lactate, has been shown to displace α-synuclein aggregates and improve symptoms of constipation in Parkinson's disease patients(5,6). It is currently unknown whether squalamine protects from other aspects of pathology in Parkinson's disease.

Objectives: The aim of this study was to determine if oral administration of the squalamine can protect from ascending pathology and motor deficits in paraquat and lectin rat model of Parkinson's disease.

Methods: Subthreshold doses of P+L were given to Sprague Dawley rats (n=33, 250-400g) via oral gavage for 7 days. An experimental group (n=17) were given squalamine in their drinking water for 30 days post-P+L treatment. A control group (n=16) received no squalamine post-P+L treatment. Motor symptoms were assessed with the vibrissae-evoked forelimb placement test (VEFPT) and stepping test at two and four weeks post-P+L treatment. Rats were euthanized and their brains were processed for histology. Tyrosine hydroxylase (TH) immunohistochemistry and Cresyl violet (CV) staining were used to determine dopaminergic neuron loss in the Substantia Nigra pars compacta (SNpc). Phospho-S129- α-synuclein (pSyn) immunohistochemistry was used to determine the presence of pathological pSyn aggregates in the SN.

Results: P+L animals showed significantly lower VEFPT and stepping test scores ($p<0.05$) at 2 and 4 weeks post-treatment compared to baseline, indicating motor deficits. Rats that received squalamine showed no significant

difference at 2 and 4 weeks post-treatment compared to baseline, indicating protection from P+L-induced motor deficits. P+L rats (n=4) show 60% dopaminergic neuronal loss in the SNpc compared to naïve control (n=1), while P+L+S rats (n=8) show only 47% dopaminergic neuronal loss in the SNpc. P+L+S rats (n=3) show non-significant decrease in phospho-S129-α-synuclein aggregates in the SN compared to P+L rats (n=3).

Conclusion: Administration of oral squalamine protects from paraquat and lectin-induced motor deficits. Literature suggests that >50% neuronal loss in the SNpc is necessary for parkinsonian motor deficits. Therefore, P+L+S rats showing <50% loss may explain protection from motor deficits compared to P+L rats. Squalamine administration post-P+L treatment suggests protection from ascending phospho-S129-α-synuclein pathology, with a nonsignificant decrease in aggregates in P+L+S compared to P+L rats. An increase in sample size and further experimentation are necessary in order to prove or disprove our hypothesis that squalamine is protective from ascending pathology in the paraquat and lectin model of Parkinson's disease.

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