Squalamine as a Potential Neuroprotective Agent in Parkinson's Disease Related Cognitive Decline

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Introduction: Parkinson's Disease (PD) is a chronic neurodegenerative condition characterized by a range of motor and non-motor clinical manifestations. Motor symptoms such as resting tremor, bradykinesia, rigidity, and postural imbalance, along with non-motor symptoms including cognitive decline, sleep disturbances, constipation, depression, and anxiety, contribute to the multifaceted nature of the disease. Among the various non-motor features under intense investigation is a cognitive decline stand out prominently. In previous research, we introduced a novel rat model of PD by administering subthreshold doses of Paraquat (P) and Lectins (L) orally. This model aimed to simulate the environmental gut-brain pathogenesis of PD, leading to associated nigral synucleinopathy and levodopa-responsive parkinsonism. Notably, protection against PD was observed through subdiaphragmatic vagotomy performed before exposure to P+L (Anselmi L et al., 2018). Studies have suggested the potential protective role of Squalamine, a natural bile salt derived from the dogfish shark, when administered orally (Perni M et al., 2017). Paraquat dichloride is a commonly used herbicide to control weeds and grass, while Lectins are carbohydrate-binding proteins found in uncooked vegetables, dairy, or eggs. Another component is cholecystokinin (CCK), a hormone produced in the small intestine that aids in the digestive process.

Objective: Our hypothesis is that animals with more severe parkinsonian motor symptoms will exhibit poorer performance in various cognitive tasks.

Methods: The Y-maze has been used extensively in animal models of PD to assess short-term memory. Twenty-five Sprague Dawley rats were placed in a Y-Maze apparatus with an overhead automated movement tracking system (AnyMaze). For five minutes, each rat's movement was tracked and scored for their independent spontaneous alternation pattern with minimal distractions. The validity of the software's output was confirmed by manual scoring. Each spontaneous alternation was reported as a raw score based on the total of triads completed in each trial. We tested this using three treatment groups: no treatment (Normal), paraquat + lectin via oral gavage (P+L), paraquat + lectin and squalamine solution (P+L+S). Within the P+L group, animals exhibited varying degrees of motor deficits as confirmed by our battery of behavioral tests.

Results: One-way ANOVA confirmed a significant difference (p=0.02) in spontaneous alternation and a value approaching significance (p=0.090) for the percent spontaneous alternation between treatment groups. Post-hoc analysis using student t-tests shows a significant difference when comparing all three P+L subcategories to normal animals. No significant difference was noted between P+L+S and normal animals. These preliminary results suggest that although motor deficits differed between animals treated with P+L, the short-term memories of these animals were equally affected regardless of the extend of the motor deficits.

Conclusion: Parkinsonian symptoms are linked to poorer maze task performance, indicating a motor-cognitive connection. Squalamine treatment improved motor symptoms and boosted maze task performance, suggesting neuroprotection.

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