Pharmacological Effects of Clozapine on GABAergic Systems and Related Secondary Structural Changes in 5-HT\(_2C\)R, of Significance to Amyotrophic Lateral Sclerosis and Cognitive Deficits in Schizophrenia

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There have been several substantiated associations between neurodegeneration and cognitive impairments associated in schizophrenia and amyotrophic lateral sclerosis (ALS). Clozapine ameliorates cognitive impairments and psychosis in schizophrenia and has been shown to prevent the onset of ALS. Thus, it has the potential to complement the only food and drug administration (FDA) approved drug for ALS. Serotonin (5-HT)\(_{2C}\) Receptor (R), is implicated in schizophrenia and is also implicated in neurodegenerative diseases like ALS; thus, we hypothesized that there could be a link between these diseases.

When clozapine was tested for its potential to reverse cognitive deficits in particular declarative memory induced by subchronic phencyclidine (PCP) in male C57BL/6J mice, using novel object recognition task, there was a significant improvement in the declarative memory. This ameliorating effect of clozapine was significantly blocked by gamma amino butyric acid (GABA)\(_A\) antagonist bicuculine.

Furthermore, the bioinformatics study showed a significant difference between the secondary structures of the healthy and diseased forms of 5-HT\(_{2C}\)Rs. There was an increase in alpha helices in the diseased protein, which has the potential to cause the overactivity of the receptor that can, in turn, instigate neuronal degredation in the central nervous system. It is concluded that clozapine has the potential to reverse cognitive deficits in schizophrenia in part due to its effect on the GABAergic system and ameliorates the cognitive impairments induced by subchronic PCP induction.