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Effects of the 5-HT_{2C} Receptor Antagonist Agomelatine on Performance in the Progressive Ratio Schedule

Schizophrenia is a mental disorder characterized by its positive, negative, and cognitive symptoms. While typical antipsychotics have been used to treat the positive symptoms of schizophrenia, there has been a dearth of effective treatment for the negative and cognitive symptoms. In order to better understand the neurobiology of schizophrenia and gain insight into new treatments, a mouse model was created to mirror the negative and cognitive symptoms of the disease. Mice in which D2 receptors have been selectively overexpressed are called D2R-OE mice, and it has been found that these mice also have higher expression levels of 5-HT_{2C} receptors in the striatum. The serotonin (5-HT) pathways in the brain have been implicated in mood, memory, and sleep — factors associated with the negative and cognitive symptoms of schizophrenia. Past research has shown that in operant tasks such as the Progressive Ratio (PR), D2R-OE mice exhibit reduced motivation to press a lever for a reward. However, administration of the drug SB-242084 — a 5-HT_{2C} receptor antagonist — improved performance on the PR for both D2R-OE and control mice, suggesting that the 5-HT_{2C} receptor may be involved in incentive motivation. Agomelatine, also a 5-HT_{2C} antagonist, has been shown to induce an antidepressant-like effect in several rodent behavioral models of anxiety and depression when injected chronically over approximately four weeks. It was hypothesized that chronic injection of 10 mg/kg agomelatine would subsequently improve the performance of D2R-OE mice on the Progressive Ratio, perhaps reflecting an increase in motivation to press a lever for a food reward. Mice were trained in operant chambers to lever press for a milk reinforcer during a three-week course of drug treatment. At the start of the fourth week of drug treatment, mice were tested on the Progressive Ratio Schedule (PR), during which the number of lever presses required to earn food was subsequently doubled after each reward (PR×2). Six consecutive test days on PR were completed; it was found that four-week-long chronic injection of 10 mg/kg agomelatine did not produce significant differences in performance between the control and D2R-OE mice. Counterintuitively, administration of agomelatine seemed to slightly impair rather than improve the performance of both control and D2R-OE mice; in particular, this effect was most salient for the control group. No significant interaction between genotype and drug condition was found. The current results suggest that (1) agomelatine may decrease the incentive motivation of mice, or that (2) agomelatine may be more apt to positively affect the behavioral responses of mice in tests of antidepressant and anxiolytic activity, rather than instrumental tests such as the Progressive Ratio.