The Role of the Endocannabinoid System in Anxiety- and Depressive-like Behaviors in Mice

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The endocannabinoid system is a group of endogenous neuromodulatory lipids and receptors that control a variety of critical physiological processes, including mood regulation and stress response. As a result, endocannabinoids are heavily implicated in many prevalent mood disorders, such as anxiety, obsessive-compulsive disorder (OCD), and depression. JZL184 is a synthetic compound that can be used to study dysregulation in the endocannabinoid system because it promotes 2-Arachidonoylglycerol (2-AG), an endogenous ligand that interacts with G-protein-coupled cannabinoid receptor CB1 [1]. Targeting these CB1 receptors with JZL184 has been shown to produce a range of therapeutic benefits, including reduced anxiety and depressive-like behaviors in mice [1, 2].

To study this system, C57BL6J mice were injected with doses of JZL 184, chlordiazepoxide (CDP), or saline solution and were introduced to a battery of anxiety tests. CDP is a benzodiazepine that is commonly used to treat many anxiety disorders, and was used as a positive control because of its well-known efficacy in mouse models of anxiety [3]. First, we employed the emergence test and the Elevated-Zero Maze (EZM) paradigms, which have been shown to effectively function as models of anxiety symptoms [4]. Both behavioral tests involve placing the subjects into an exposed environment and monitoring the subjects’ anxious versus exploratory behaviors. The duration of time spent hidden in the enclosed area of the maze was measured and compared to the amount of time spent exploring the exposed, open area of the maze. Avoiding these exposed areas and hiding in the enclosed region has been shown to be demonstrative of anxiety-like behaviors [4]. It was found that CDP had no effect on the emergence test or EZM, and JZL184 significantly increased anxiety-like behaviors in the emergence test but had no effect in the EZM. These results seem to suggest that dysregulation of the endocannabinoid system can influence symptoms of anxiety.

The third experiment within this battery was the marble burying test, which is a commonly utilized mouse model for measuring obsessive-compulsive-like tendencies in mice. Mice have been shown to instinctively bury foreign objects into the ground as an anxious and obsessive tendency, and this action has been shown to reduce when given medications used to treat OCD [5]. Consistent with our hypothesis, it was found that both CDP and JZL 184 significantly decreased the number of marbles buried, suggesting a reduction in obsessive-compulsive like behaviors.

In a follow up study, we examined depressive-like behaviors using the Forced Swim Test (FST) in a separate sample of mice. The FST is the most commonly used model of depression in rodent research, and works by measuring the amount of time mice spend floating still versus swimming in a small beaker of water [2]. Several studies have provided evidence for the antidepressant-like effects of cannabinoids in the FST [6, 2], however, we were not able to replicate these findings in our preliminary trials, where we found no significant differences in swim time for JZL184 or CDP. Despite these inconclusive findings for depressive behaviors, we found that overall, drugs targeting the endocannabinoid system shows great promise as a potential treatment option for emotion regulation and mood disorders.
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References


