The Cannabinoid 1 Receptor Allosteric Modulator GAT211 Impacts Behavior in a Sex-Dependent Manner

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Background: Drugs that target the endocannabinoid system are gaining significant attention in the field of neuropharmacology. Cannabinoid 1 Receptors (CB1Rs) are of special interest due to their implication in a wide array of neuropsychiatric disorders. Allosteric modulators (AMs) of the Cannabinoid 1 Receptor (CB1R) alter endocannabinoid binding at the orthosteric binding site. CB1R AMs present a promising new avenue for the development of therapeutics. However, sex differences in the endocannabinoid system have been detailed in a growing body of literature. Despite this, few research studies have examined whether sex impacts the efficacy of CB1R AMs.

Methods: GAT211 is an allosteric agonist and positive AM of CB1Rs. This compound increases the binding of endocannabinoids to CB1Rs. In the present study, male and female mice were given I.P. injections of either GAT211 or vehicle and tested on the elevated plus maze (EPM) and open field test (OFT).

The EPM is a behavioral test that is used to test anxiety behaviors. The OFT is used to assess locomotion and exploratory behavior.

Results: Male mice exposed to GAT211 spent significantly more time in the open arms of the elevated plus maze when compared to mice within the control group. Female mice exposed to GAT211 performed similarly to both male and female control animals. There was no significant difference on the open field test, which suggests that GAT211’s effect on males is not simply the result of increased locomotion.

Conclusion: These findings suggest that the effects of CB1R AMs may be sex-dependent. This presents an important consideration for evaluating the translational potential of these molecules. Furthermore, the results presented here highlight the importance of research examining sex as a biological variable.