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Pharmacological inhibition of the primary endocannabinoid producing enzyme, DGL-α, induces ASD and co-morbid ASD phenotypes in adult C57BL/J mice

Accumulating evidence links dysfunction in the endocannabinoid system (ECS) with the pathology of neurodevelopmental disorders, particularly Autism Spectrum Disorder (ASD). Variants in endocannabinoid system genes CNR1 and DAGLA have been associated with neurological phenotypes in humans. The endocannabinoids (eCBs), 2-AG and AEA, which act at the primary cannabinoid receptor (CB1), mediate behaviors relevant to neurodevelopmental disorders. The overlap between these two eCBs is poorly understood. Most ECS studies have focused on stress responses, anxiety, and epilepsy, however its role in social behavior and communication has only recently come under investigation. This represents a critical gap in our understanding of the ECS and its relationship to ASD. Furthermore, the increasing prevalence of ASD and a lack of therapeutics emphasize a crucial need for novel therapeutic targets. To this aim, we used a highly selective inhibitor of the eCB producing enzyme DGL-α, DO34, and the CB1 inverse agonist, rimonabant, to evaluate the role of the primary eCB, 2-AG, in ASD. Adult male C57BL/6J mice were used in a series of behavioral paradigms which assessed social behavior, social communication, repetitive behaviors, anxiety and locomotor activity. Both DO34 and rimonabant increased anxiety-like behavior, while only DO34 induced hyperactivity, social deficits, and repetitive self-grooming behavior. These data indicate that reduced 2-AG bioavailability, but not CB1 inhibition, play a role in behavioral phenotypes relevant to neurodevelopmental disorders, particularly ASD. This suggests there are fundamental differences in CB1 signaling, particularly for social behaviors, and that 2-AG signaling may represent a target for the development of novel therapeutics.

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