Alterations in Neuromodulatory Proteins in Single APP Knock-in Mice Assessed Following Ketamine Therapy

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Alzheimer's disease (AD) poses a global health challenge, necessitating a deeper exploration of its etiology for effective interventions. This study investigates the impact of ketamine, an NMDA receptor antagonist, on neuromodulatory proteins in the context of AD using App knock-in mice, enhancing translational relevance. Neuromodulatory pathways, including glutamate, GABA, BDNF, and the mTOR signaling pathway, are central to cognitive processes and often dysregulated in AD. Ketamine's potential therapeutic effects are explored through behavioral tests assessing recognition memory (novel object recognition), depressive behavior (forced swim test), and spatial memory (Y-maze). Ketamine treatment in the App Ketamine group led to significant alterations in neuromodulatory complexes in the prefrontal cortex (PFC), hippocampus (HPC), and amygdala (AMY). IHC quantification and Western Blot assays were performed using primary antibody solutions and after fractioning isolated MF hippocampal proteins by SDS-polyacrylamide gel electrophoresis. In the PFC, ketamine induced an increase in glutamate, a decrease in glutamine, and a reduction in GABA levels, showcasing its impact on neurotransmitter systems. The hippocampus exhibited elevated BDNF levels, reduced GSK-3, and increased PSD-95, suggesting ketamine's potential to enhance synaptic plasticity. The amygdala, linked to emotional processing, displayed decreased BDNF and AMPA GluA1 levels. Behavioral assessments revealed ketamine and genotype-induced improvements in recognition memory, cognitive flexibility, and depressive-like behavior. The study emphasizes the need for personalized therapeutic strategies, due to the interplay between ketamine, genetics, and neuromodulatory pathways in the pursuit of effective AD treatments.

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