

# **Synergistic Effects of Intranasally Administered GALR2 and Y1R Agonists on Cognitive and Mood-Related Behaviors in Adult Rats: Implications for Neurodegenerative and Mood Disorders**

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## **Abstract**

**Background:** The complexity of neurodegenerative and mood disorders necessitates innovative therapeutic strategies beyond current treatments. This study explores the combined therapeutic potential of Galanin receptor 2 (GALR2) and Neuropeptide Y Y1 receptor (Y1R) agonists, administered intranasally, on spatial memory, antidepressant-like behavior, and neurogenesis in adult rats.

**Methods:** The investigation employed intranasal co-delivery of GALR2 agonist M1145 and Y1R agonist to adult rats, examining spatial memory through the object-in-place task and antidepressant-like effects via the Forced Swimming Test. Neuronal survival and differentiation were assessed by BrdU-IR profiles, doublecortin (DCX) labeling, and Proximity Ligation Assay (PLA) for GALR2/NPY1R heteroreceptor complexes in the hippocampus.

**Results:** Co-administration significantly improved spatial memory and exhibited antidepressant-like behaviors. Notably, the presence of GALR2/NPY1R heteroreceptor complexes in the ventral hippocampal dentate gyrus was associated with these behavioral outcomes. Enhanced neuronal survival, increased proliferation of neuroblasts, and augmented DCX-positive cell numbers with mature dendritic morphology were observed, suggesting enhanced neurogenesis and neuronal differentiation.

**Conclusions:** The synergistic action of GALR2 and Y1R agonists via intranasal delivery offers a promising therapeutic approach for improving cognitive function and mood, highlighting the potential for new treatment strategies in neurodegenerative and mood disorders. The critical role of GALR2 in these processes suggests a novel target for future pharmacological interventions.

## **Keywords**

GALR2 agonist, NPY1R agonist, spatial memory, antidepressant-like behavior, neurogenesis