Unveiling the Synergistic Interplay of Neuropeptides for Novel Therapeutic Approaches in Neurodegenerative and Depressive Disorders

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The intricate relationship between hippocampal neurogenesis dysregulation and neurodegenerative diseases such as Alzheimer's, as well as depression, has sparked an urgent call for innovative therapeutic strategies. Our groundbreaking study delves into the interaction of Neuropeptide Y (NPY) and galanin (GAL) agonists, two neuromodulatory systems with a substantial presence in the limbic system, and their potential neurogenic impact on both the dorsal and ventral hippocampus.

Through meticulous examination of the subchronic effects of NPY Y1 (Y1R) and GAL2 (GALR2) agonists on hippocampal cell proliferation, survival, and neuroprotective factor expression, we reveal a fascinating cascade of cellular responses. These include increased cell proliferation (PCNA), enhanced hippocampal cell survival (BrdU), and induction of neuroprotective factors (BDNF).

Our functional assessment showcases the resulting improvements in spatial memory performance in the object-in-place task and antidepressant-like effects in the forced swimming test. These outcomes are attributed to the synergistic interaction between Y1R and GALR2 receptors, which promote neuronal survival and neurite outgrowth in hippocampal cells.

This pioneering research paves the way for the development of heterobivalent agonist pharmacophores that target Y1R-GALR2 heterocomplexes. By acting on neuronal precursor cells in the dentate gyrus of the dorsal hippocampus, these novel compounds hold immense promise as transformative therapies for cognitive and affective impairments in neurodegenerative and depressive diseases.