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Combined administration of scopolamine and a negative allosteric modulator of the metabotropic glutamate mGlu2 receptor as a novel efficacious method to treat depression

Summary of Doctoral Dissertation

Major depressive disorder (MDD) is widely recognized as one of the most prevalent and debilitating mental health problems. Despite the availability of numerous conventional antidepressants primarily targeting the monoaminergic system, they are far from ideal and often produce delayed and only partial relief. Consequently, the need for more effective and rapid-acting compounds is as timely and compelling as ever.

Numerous clinical and preclinical studies indicate that scopolamine, a non-selective muscarinic cholinergic receptor antagonist, exerts rapid and long-lasting antidepressant effects. However, its clinical use is limited by considerable adverse effects, including memory impairment, sedation, and visual disturbances. One potential strategy to mitigate these adverse effects is the coadministration of scopolamine at low doses with other compounds that possess antidepressant properties. This therapeutic approach was implemented in the present doctoral thesis, wherein subeffective doses of scopolamine were combined with subeffective doses of the mGlu2 negative allosteric modulator (NAM) VU6001966.

All experiments were conducted on male C57BL/6J mice or Sprague Dawley rats. To evaluate the antidepressant-like effects of the tested combination, a chronic stress-based mouse model of depression — the unpredictable chronic mild stress (UCMS) paradigm — was employed. This model enables the assessment of parameters that reflect core depressive symptoms and the distinction between classical and rapid-acting antidepressants. These behavioral parameters included reduced grooming time in the splash test, indicating apathy; decreased sucrose preference in the sucrose preference test (SPT), serving as a measure of anhedonia; and increased immobility in the tail suspension test (TST) and the forced swim test (FST), reflecting behavioral despair.

To explore the mechanisms underlying the observed effects, the AMPA receptor antagonist NBQX and TrkB receptor antagonist ANA-12 were used to determine the involvement of these receptors in antidepressant-like action. Additionally, the role of mTOR and BDNF/TrkB signaling pathways was investigated by measuring the expression levels of

selected proteins using the Western Blot technique.

To evaluate the risk of potential adverse effects from the tested combination, we conducted a locomotor activity test to assess general activity, as well as object location (OLT) and novel object recognition (NORT) tests to assess memory.

Moreover, microdialysis in freely moving rats was used to examine the effects of the compounds on extracellular levels of key neurotransmitters (serotonin, dopamine, glutamate, and GABA) in the rat frontal cortex (FCX).

The results support the notion that combining scopolamine with the mGlu2 NAM VU6001966 not only enhances its antidepressant efficacy but may also attenuate adverse effects commonly associated with scopolamine use. Subchronic coadministration of scopolamine and VU6001966 over four consecutive days did not impair locomotor activity or spatial and non-spatial memory. Furthermore, the acute antidepressant-like effects were associated with increased extracellular levels of glutamate, dopamine, and serotonin in the frontal cortex, whereas sustained effects following subchronic treatment appeared to depend on AMPA and TrkB receptor activation.

In summary, the coadministration of scopolamine with the mGlu2 NAM VU6001966 may offer significant clinical potential by allowing lower therapeutic doses of scopolamine while preserving cognitive function. Nonetheless, some limitations must be acknowledged. Given the possibility of interspecies and sex differences, findings from these preclinical studies should not be directly extrapolated to the human condition of depression.