Combinations of Buprenorphine and Samidorphan Modulate Glutamatergic Transmission in the Medial Prefrontal Cortex and Ventral Hippocampus of Male Wistar Rats

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**INTRODUCTION**

Excessively high or low levels of glutamate and GABA in the brain result in neurodegenerative disorders like schizophrenia and Alzheimer’s disease. While clinical treatment options for these disorders are available, they often suffer from side effects. Thus, there is a need for alternative treatment options, ideally with reduced off-target effects and improved efficacy. We hypothesized that combining Buprenorphine (BUP), an opioid agonist, with Samidorphan (SAM), a GABA\(\alpha_1\) antagonist, would produce a synergistic effect and modulate glutamatergic transmission.

**METHODS**

Experiments were conducted in accordance with the guidelines of the Guide for the Care and Use of Laboratory Animals. Procedures involving animals were approved by the institutional animal care and use committee (IACUC).

**RESULTS**

BUP produced a delayed increase in Glu concentrations in the mPFC, which was alleviated by SAM. SAM alone was not able to affect Glu levels. The combination of BUP + SAM produced a decrease in GABA concentrations in the mPFC.

**CONCLUSIONS**

BUP administration resulted in an increase in extracellular concentrations of Glu in the mPFC of Wistar rats. The timing of the increase in mPFC Glu produced by BUP suggests that this occurs via indirect activation of neurochemical pathways.

BUP and SAM modulated concentrations of mPFC Glu and HIPPP GABA.

Controlled modulation of monoamine and amino acid neurotransmitter systems may contribute to the efficacy of ALKS 5461 in the treatment of depression.

**DISCLOSURES**

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