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Short abstract: Depression and opioid use disorder (OUD) represent major public health challenges with limited treatment options. We investigated the therapeutic potential and mechanistic basis of ketamine and its metabolites, across both conditions using behavioral, electrophysiological, and molecular approaches in mice. We demonstrate that NMDA receptor activation, rather than inhibition, is essential for rapid antidepressant effects. Ketamine exhibited an inverted U-shaped dose-response relationship, and its antidepressant-like properties, hippocampal AMPA receptor upregulation, and metaplasticity induction were abolished by NMDA receptor antagonist pre-treatment. ketamine's metabolites, (2R,6R)-Hydroxynorketamine and other rapid-acting antidepressants required NMDA receptor signaling, with the GluN2A subunit being both necessary and sufficient for these actions. In OUD models, (2R,6R)-HNK effectively countered morphine conditioning in stress-vulnerable mice, prevented withdrawal symptoms, and alleviated anhedonia, anxiety, and cognitive deficits during protracted abstinence. Importantly, it enhanced extinction of opioid conditioning, blocked stress-triggered relapse, and reduced subsequent opioid consumption possibly by restoring disrupted cortical high-frequency EEG oscillations. These findings reveal a convergent mechanism whereby (2R,6R)-HNK promotes GluN2A-NMDAR-dependent synaptic plasticity to provide rapid antidepressant effects while addressing negative affect and relapse vulnerability in OUD.

Lab website link: www.zanoslab.com

Short Biosketch: Dr. Panos Zanos is an Assistant Professor of Neuropharmacology at the University of Cyprus, where he serves as a Principal Investigator since August 2021. He is also the Founder and President of the Cyprus Neuroscience Society. Dr. Zanos received his Ph.D. in Neuropharmacology from the University of Surrey, UK, in 2013, followed by postdoctoral training at the University of Maryland School of Medicine. Prior to his current position, he served as Assistant Professor of Neuroscience at the University of Maryland (2019-2021). His research focuses on understanding the neurobiological mechanisms underlying rapid-acting antidepressants, particularly ketamine and its metabolites, and developing novel pharmacotherapies for comorbid substance use and mood disorders. Dr. Zanos has published extensively in journals including *Nature*, *Nature Neuroscience*, *PNAS*, *Biological Psychiatry*, and *Molecular Psychiatry*, and holds multiple patents for therapeutic applications of ketamine-related compounds. Dr. Zanos has received numerous awards, including the University of Cyprus Best Researcher Award (2025), the Marie Skłodowska Curie Young Investigator Fellowship, and the Best Postdoctoral Scholar Award from the University of Maryland. He serves as a reviewer for leading neuroscience journals and as a grant panel member for international funding agencies. His research is supported by multiple active grants exceeding €2.5 million in total funding.