PHARMACEUTICAL SCIENCES
JAMES L. WINKLE COLLEGE OF PHARMACY

SUMMER RESEARCH OPPORTUNITIES FOR UNDERGRADUATE students

FOR APPLICATION YEAR: 2025

PROJECT TITLE: Astroglial mechanisms underlying primary antipsychotic resistance

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Project Description

Antipsychotics are prescribed to treat psychiatric illnesses including schizophrenia and bipolar disorder. Despite being widely used, antipsychotics lack efficacy in one third of patients with first-episode psychosis who experience persistent symptoms and are therefore said to experience primary antipsychotic resistance. This subgroup of patients often undergo treatment with second-line medications like clozapine, a superior antipsychotic that carries serious life-threatening side effects. Importantly, the molecular mechanisms underlying primary antipsychotic resistance are unknown. We found that chronic cocaine self-administration in rats increased resistance to the sedative effects of the antipsychotic haloperidol, but not clozapine. This effect was largely driven by downregulation of the glutamate (GLT-1) and dopamine transporter (DAT) in the nucleus accumbens. While both haloperidol and clozapine increased astrocyte motility toward glutamatergic synapses in the accumbens, clozapine alone increased surface diffusion of GLT-1. Clozapine also caused astrocytes to retract from dopaminergic synapses. We hypothesize that the consequence of clozapine-induced astrocyte plasticity will be suppression of excitatory signaling and enhanced monoaminergic signaling. Moving forward, we will test for the effects of clozapine-induced astroglial adaptations on extracellular transmitter levels and synaptic activity.