PHARMACEUTICAL SCIENCES
JAMES L. WINKLE COLLEGE OF PHARMACY

SUMMER RESEARCH OPPORTUNITIES FOR UNDERGRADUATE students

FOR APPLICATION YEAR: 2026

PROJECT TITLE: Astroglial mechanisms underlying primary antipsychotic resistance

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Project Description

Antipsychotics are used to treat various psychiatric symptoms, including psychosis, yet symptoms persist in one-third of patients with first-episode psychosis due to antipsychotic resistance (AR). These patients require second-line agents like clozapine, which may cause serious side effects. The molecular basis of AR remains unknown, limiting development of safer alternatives. Use of addictive drugs, including psychostimulants, is a known risk factor for AR. We propose that reduced expression of dopamine and glutamate transporters (DAT, GLT-1), key regulators of striatal neurotransmission, may predispose individuals to AR. Male and female Long Evans rats (200-250 g) were trained to self-administer cocaine or sucrose. Antipsychotic efficacy was measured as the ability to Inhibit locomotor activity induced by dopamine-based tail pinch assay and by low-dose ketamine (30 mg/kg i.p.), known to induce positive and negative-like schizophrenia symptoms in humans. Clinically relevant doses of haloperidol (0.2 mg/kg) or clozapine (15 mg/mg) were given before testing. To test causality, rats received nucleus accumbens core (NAcore) infusions of control or morpholino oligomers targeting DAT or GLT-1 for 3 days. After incubation, behavioral and protein analyses were conducted. Blinding and replication were included. To probe the neurophysiology of clozapine’s efficacy despite transporter loss, we examined astrocytic regulation of glutamate and dopamine synapses in the NAcore. Haloperidol suppressed hyperlocomotion in control rats, but was ineffective after chronic cocaine use (p