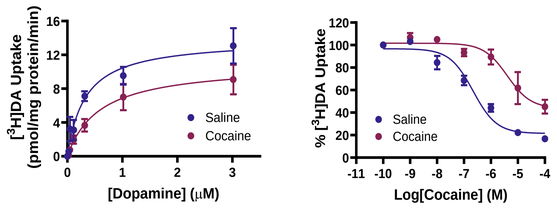
Membrane Cholesterol Depletion Alters Striatal Dopamine Homeostasis and Dopamine-Associated Behavior

Anna I. Neel, Alyssa M. West, Kimberly M. Holter, Monica H. Dawes, Katherine E. Liontis, Robert W. Gould, Sara Jones, & Rong Chen
Department of Translational Neuroscience, Wake Forest University School of Medicine, Winston-Salem, NC

INTRODUCTION

- Chronic cocaine use results in the dysregulation of dopamine transporter (DAT) function and synaptic dopamine transmission, which contributes to enhanced drug-taking and -seeking



- While the mechanisms underlying cocaine-induced DAT dysfunction remain elusive, emerging evidence suggests a potential link between DAT function and brain cholesterol
- Brain cholesterol regulates the function of membrane proteins through protein-cholesterol interactions or by altering membrane fluidity, which modulates protein conformation
- Whether cocaine dysregulates DAT function by disrupting cholesterol homeostasis has not been explored

HYPOTHESIS

Cocaine self-administration significantly alters brain cholesterol homeostasis, which contributes to the altered dopamine (DA) transmission and DAT function observed with cocaine exposure

METHOD

Cocaine Self-Administration: Male Sprague-Dawley rats self-administered 40 injections of cocaine (1.5 mg/kg/inf, 6 h/d) or saline for 5 days on an FR1 schedule

Assessment of Cholesterol Metabolism: Membrane (bioactive) cholesterol content was measured via an Amplex Red assay. 24(S)-hydroxycholesterol levels were determined via an ELISA kit

Chronic Cholesterol Depletion: Male Sprague-Dawley rats were implanted with an osmotic minipump delivering the cholesterol synthesis inhibitor simvastatin (5 mg/kg/d) or vehicle for 14 d

Acute Cholesterol Depletion: Once the evoked extracellular DA response was stable, methyl-β-cyclodextrin (MβCD), a membrane cholesterol chelator, was perfused over brain slices for one hour, followed by washout

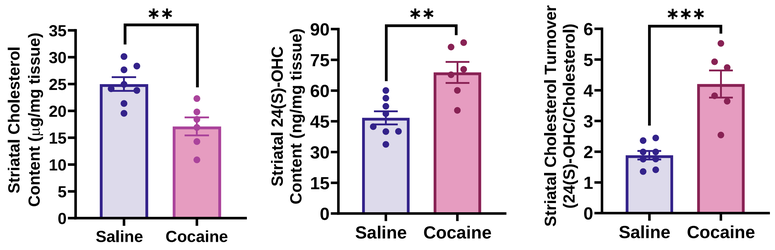
Ex-Vivo Fast-Scan Cyclic Voltammetry: Recording and stimulating electrodes were placed in the NAc core, and an electrical pulse (4ms, 750 μA) evoked DA release and reuptake; DA kinetics were determined using Michaelis-Menten modeling

CONCLUSIONS

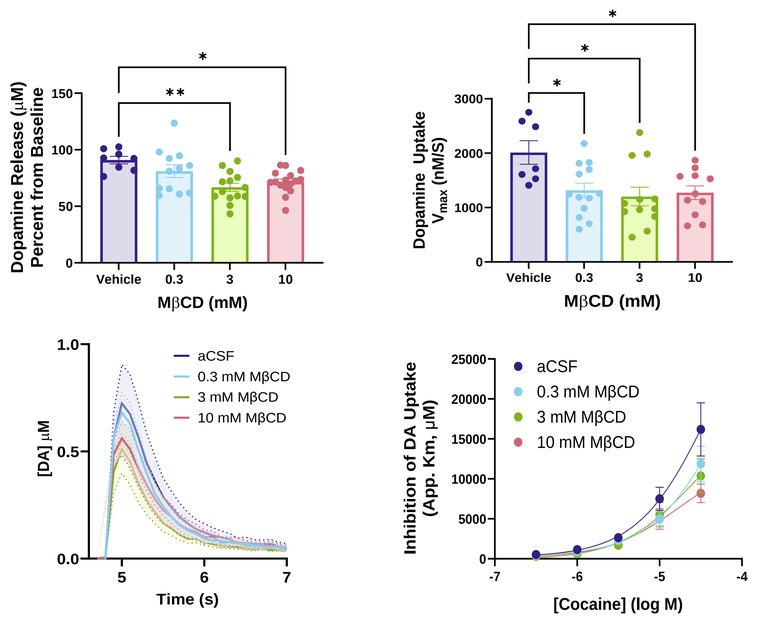
- Acute and chronic cholesterol depletion reduces dopamine release, DAT function, and the ability of cocaine to inhibit DAT
- The dysregulation of dopamine dynamics by cholesterol depletion may be mediated by disruption of the actin cytoskeleton
- The proper conformation and function of membrane proteins is also regulated by the cortical actin cytoskeleton, which closely interacts with membrane cholesterol to modulate protein function
- Altered brain cholesterol metabolism may underlie cocaine-induced neuroadaptations to dopamine homeostasis and DAT dysfunction
- These findings underscore the potential of CUD pharmacotherapies aimed at restoring cholesterol homeostasis and the imaging of brain cholesterol as a biomarker for CUD

RESULTS

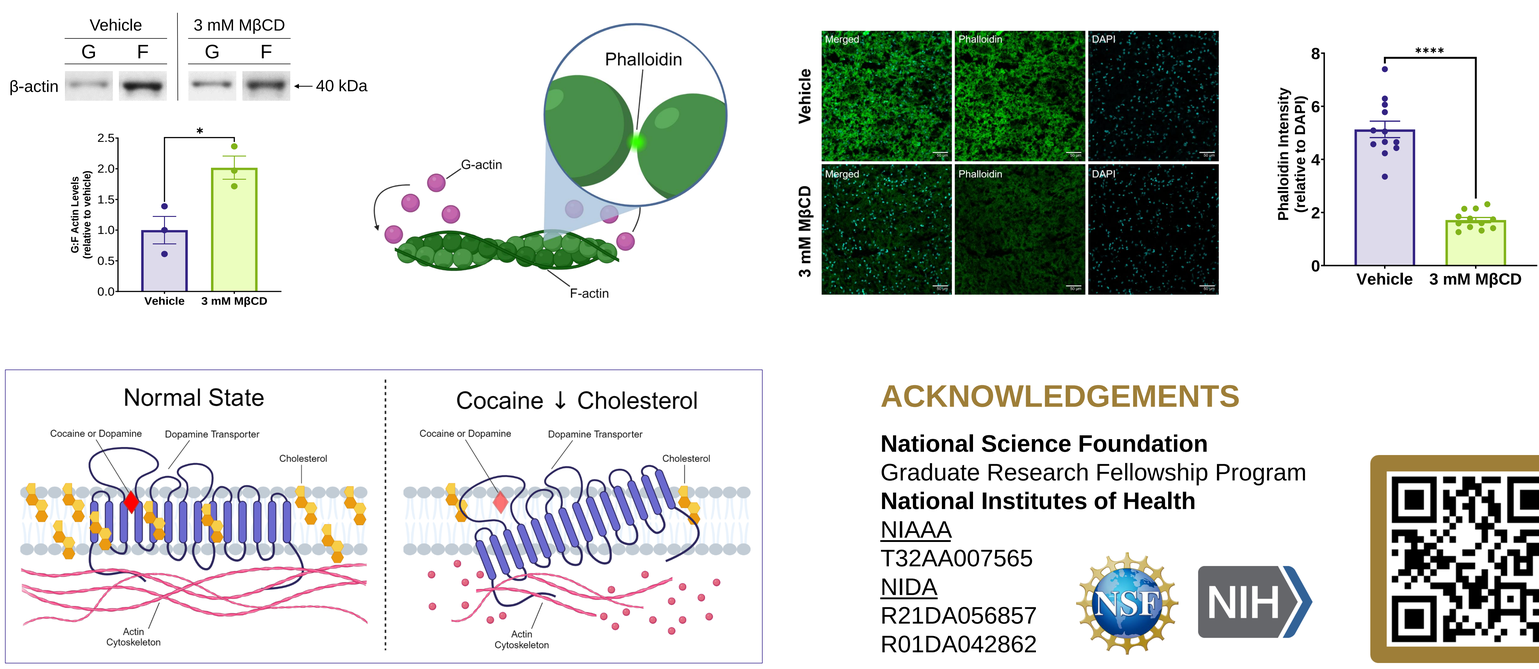
1. Cocaine self-administration decreases striatal cholesterol content via increased cholesterol turnover



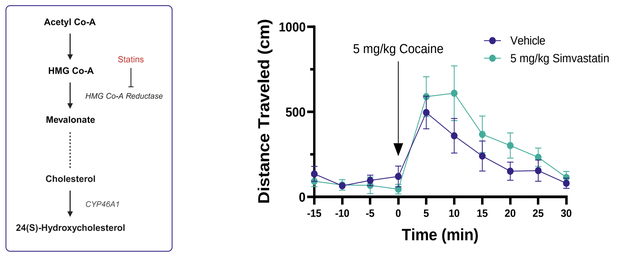
2. Acute membrane cholesterol depletion via methyl-β-cyclodextrin (MβCD) dysregulates dopamine terminal dynamics



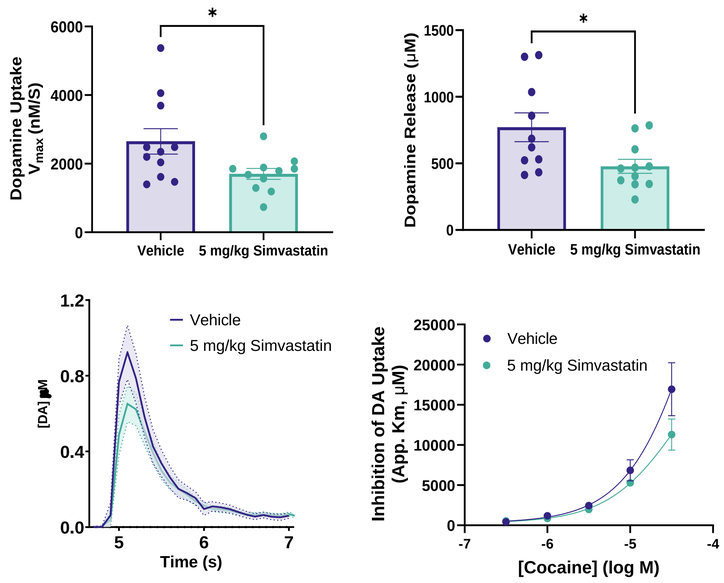
3. Acute membrane cholesterol depletion via methyl-β-cyclodextrin reduces actin cytoskeleton polymerization



4. Simvastatin, a cholesterol-lowering drug, enhances cocaine-induced locomotor activity



5. Chronic cholesterol depletion via simvastatin dysregulates dopamine terminal dynamics



ACKNOWLEDGEMENTS

National Science Foundation
Graduate Research Fellowship Program
National Institutes of Health
NIAAA
T32AA007565
NIDA
R21DA056857
R01DA042862