Name: Mudit Tyagi
PI Name: Jarin Hongpaisan

Email: mudit.tyagi@jefferson.edu
PI Email: jarin.hongpaisan@jefferson.edu

Effect of Cocaine, Human Immunodeficiency Virus (HIV) Tat Peptide, and Antiretroviral Drugs on Human Brain Microvascular Endothelial Cells

Mudit Tyagi, Adhikarimayum Lakhikumar Sharma, Jarin Hongpaisan

Department of Medicine, Center for Translational Medicine, Thomas Jefferson University, 1020 Locust Street, Jefferson Alumni Hall, Philadelphia, PA, 19107, USA

Cocaine misuse further exacerbates the development of cerebral small vessel disease, which remains understudied, especially in the context of HIV. The effect of cocaine, HIV transactivator of transcription (Tat) peptides, and retroviral (ART) drugs were therefore studied in human brain microvascular endothelial cell cultures. A single low-dose cocaine (5 or 10μM) treatment induced a temporarily increase in cytosolic Ca2+, cytosolic and mitochondrial superoxide (O2•-), and the apoptotic marker cleaved caspase-3. After repeated treatment (twice per day) for 6 days, low-dose cocaine (5-10μM) induced a prolonged increase in superoxide production and cell over-proliferation that was associated with an increase in the vascular endothelial growth factor (VEGF) molecular targets [extracellular signal-regulated kinase1/2 (ERK1/2) and phosphor-Akt1 kinase] and mitochondrial transcription factor (TFAM). However, repeated and high-dose cocaine (20μM) decreased protein kinase C epsilon and ERK1/2 cascade, resulting in endothelial cell loss. Moreover, HIV-Tat (1μg/ml) with and without the ARTs induced an oxidative stress-dependent increase in endothelial cells, that was inhibited by the HIF-1α inhibitor echinomycin. This indicates that HIV-Tat with or without ARTs induces sustained hypoxia pathway. For endothelial membrane permeability test, HIV-Tat or low-dose cocaine (10μM) alone had no effect, but treatment of Tat and cocaine together rapidly induced blood-brain-barrier (BBB) leaking that was inhibited with the antioxidant N-Acetyl-Cysteine (Nac). Basically, cocaine at psychoactive dose induces vasoconstriction, leading to an increase in microvascular density. In conclusion, the results show that the adaptive effect of cocaine on angiogenesis is switched to microvascular damage under HIV infection with ART treatment.