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Combined Effects of Drugs of Abuse and HIV Infection Comorbidity on Primary Pericytes

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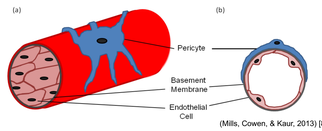
Abstract

Background: Pericyte cells are an integral component of the vascular system and blood-brain barrier. HIV infection has been shown to impact both pericytes and the blood-brain barrier. Similarly, drugs of abuse have been found to alter blood-brain barrier permeability. Drugs of abuse and HIV infection comorbidity may affect pericyte function and viral replication.
Methods: Pericyte cells were treated with varying concentrations of either morphine, cocaine, or methamphetamine to determine cytotoxicity. Next, two concentrations were chosen and infected with macrophage tropic SHIV-BORI159N4. Viral supernatant was collected every three days for analysis viral titer using qPCR and other inflammatory markers.
Results: Drug treatment appeared to impact viral replication in pericyte cells. Most drug treatments produced lower viral titers, except for the methamphetamine at 10μM concentration treatment.
Conclusion: Drugs of abuse may impact how HIV infection affects pericyte cells, though underlying mechanisms are still not well-defined. Various classes of drugs may differentially alter viral replication within pericyte cells.

Introduction



(Mills, Cowen, & Kaur, 2013) [8]

Pericytes are cells embedded in capillary walls throughout the body, including the brain [1]. They are an integral component of the circulatory system and play a role in vascular regulation and blood-brain barrier modulation. Within the brain, pericytes act as part of a neurovascular unit to regulate cerebral blood flow and maintain the blood-brain barrier, along with neurons, astrocytes, microglia, endothelial cells, and more [1].

Previous studies have shown that HIV is able to migrate through the blood-brain barrier and infect cells of the central nervous system, causing damage, cell death, and neurodegenerative disorders [2]. Furthermore, HIV infection has been shown to impact the integrity of the blood-brain barrier [3]. As HIV can infect pericytes and disrupt pericyte function [4,5], virus-mediated attack on pericytes and the blood-brain barrier may be one mechanism in which HIV is able to enter the brain.

Further, drugs of abuse, such as cocaine, methamphetamine, and morphine, have all been found to disrupt the blood-brain barrier by altering permeability [6]. HIV and drugs of abuse often present as comorbidities. This can be the result of painkiller drugs prescribed for HIV-related symptoms, risky behaviors during drug use such as sharing injection equipment that elevates HIV contraction risk, or other behaviors. Therefore, our studies plan to explore HIV and drugs of abuse as comorbidities to understand their impact on each other and the underlying mechanisms.

Previous Findings

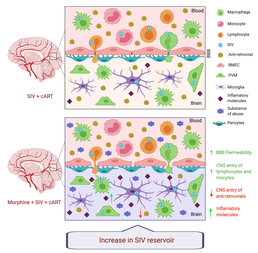


***Figure 1** (left). Diagram illustrating effects of morphine and cART on SIV-infected rhesus macaque models*

- Previous study from our laboratory found that combination of morphine and antiretroviral therapy (cART) led to larger latent SIV reservoir size in the central nervous system [7]
- Morphine and cART led to increased blood-brain barrier permeability through increases in pro-inflammatory cytokines

Materials and Methods

	Concentrations of drugs used (μM)
Morphine	1, 10
Cocaine	1, 10
Methamphetamine	10, 100

***Figure 2** (left). Table specifying concentrations of drugs of abuse used in experiment.*
***Figure 3** (right). Diagram illustrating experimental setup of 24-well plate for drug treatment and HIV infection.*

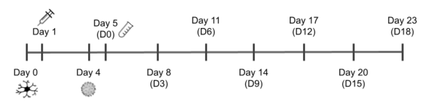


***Figure 4.** Timeline for experimental setup. Day 0—seed cells in 24-well plate; day 1—treat cells with drugs; day 4—infect cells with SHIV-BORI; day 5 (day 0 sup collection)—wash cells and collect viral supernatant; day 8 onwards—collect viral sup every 3 days for analysis.*

Primary pericyte cells were seeded in a 24-well plate. They were treated with corresponding, predetermined concentrations of either morphine, cocaine, or methamphetamine dissolved in deionized water. After the initial drug treatment, the pericytes were infected with 1MOI of SHIV-Bo199N4 for 24 hours. After washing, viral supernatant was collected from each well every three days, and media and drugs were replenished. The viral supernatant was then analyzed via qPCR for viral titer measurements. Further analysis will be performed for inflammatory cytokines/chemokines.

Results

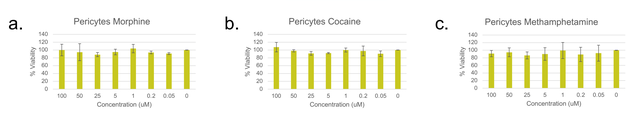


***Figure 5.** Graphs showing cytotoxicity for pericyte cells at various concentrations of drugs: a.) morphine, b.) cocaine, c.) meth. Concentrations for this experiment were chosen based on low cytotoxicity to simulate effects of drugs without excess cell death*

Results

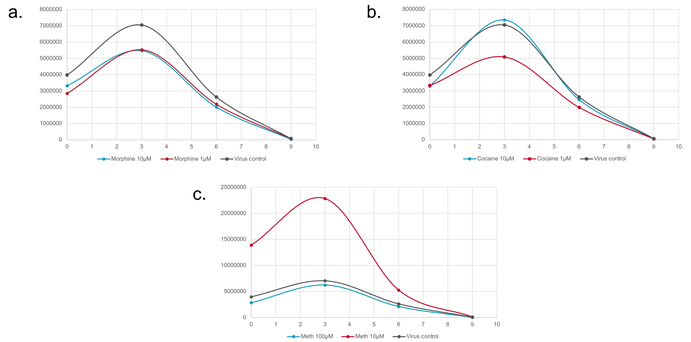


***Figure 6.** Graphs illustrating viral titer measurements for pericytes treated with varying concentrations infected with SHIV for: a.) morphine, b.) cocaine, c.) methamphetamine.*

- Drug treatment of methamphetamine at 10μM resulted in highest viral titer load
- Other drug treatments and concentrations show lower viral titer compared to non-treated infected cells
- Highest viral loads at day 3 post-infection

Conclusions and Future Direction

Conclusions
- Treating with drugs of abuse altered viral replication of SHIV in pericyte cells
- Drugs appear to lower viral replication, except with methamphetamine at 10μM concentration

Future Steps
- Experiment with antiretroviral therapy treatment post-infection is planned.
- Test drug treatment and HIV infection on other types of cells (astrocytes, microglia, etc.)
- Test additional drug classes for commonly abused drugs
- Test effect of polydrug combinations in astrocytes, microglia and pericytes in the context of HIV infection and possibly *in vivo* studies using macaque models.

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