Submitter Name: Nazira El-Hage
Submitted email: nelhage@fiu.edu

Morphine counteracts the antiviral effect of antiretroviral drugs and causes upregulation of p62/SQSTM1 and histone modifying enzymes in HIV-infected astrocytes

Myosotys Rodriguez[1], Jessica Lapierre[1], Chet Raj Ojha[1], Shashank Pawitwar[1], Mohan Kumar Muthu Karuppan[1], Fatah Kashanchi[2], and Nazira El-Hage[1]

[1]Department of Immunology, Herbert Wertheim College of Medicine, Florida International University; [2]Laboratory of Molecular Virology, School of Systems Biology, George Mason University

Accelerated neurological disorders are increasingly prominent among the HIV-infected population and are likely driven by the toxicity from long-term use of antiretroviral drugs. We explored potential side-effects of antiretroviral drugs in HIV-infected primary human astrocytes and whether opioid co-exposure exacerbates the response. HIV-infected human astrocytes were exposed to the reverse transcriptase inhibitor, emtricitabine alone or in combination with two protease inhibitors **r**itonavir and **a**tazanavir (ERA) with and without morphine co-exposure. The effect of the protease inhibitor, **l**opinavir alone or in combination with the protease inhibitor, **a**bacavir and the integrase inhibitor, **r**altegravir (LAR) with and without morphine co-exposure was also explored. Exposure with emtricitabine alone or ERA in HIV-infected astrocytes caused a significant decrease in viral replication and attenuated HIV-induced inflammatory molecules, while co-exposure with morphine negated the inhibitory effects of ERA, leading to increased viral replication and inflammatory molecules. Exposure of FTC alone or in combination with morphine caused a significant disruption of mitochondrial membrane integrity. Genetic analysis revealed a significant increase in the expression of p62/SQSTM1 which correlated with an increase in the histone-modifying enzyme, ESCO2, after exposure with ERA alone or in combination with morphine. Furthermore, several histone-modifying enzymes such as CIITA, PRMT8 and HDAC10 were also increased with LAR exposure alone or in combination with morphine. Accumulation of p62/SQSTM1 is indicative of dysfunctional lysosomal fusion. Together with the loss of mitochondrial integrity and epigenetic changes, these effects may lead to enhanced viral titer and inflammatory molecules contributing to the neuropathology associated with HIV.