Differential in vitro Neurotoxicity of Antiretroviral Drugs

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BACKGROUND

HIV-Associated Neurocognitive Disorders (HAND) - Life expectancy of HIV (+) patients in the U.S.A is expected to be similar to that of uninfected individuals.
- Persistence of HIV-Associated Neurocognitive Disorders (HAND) is an unexpected finding, affecting up to 50% of infected patients in the era of suppressive antiretroviral therapy (ART).
- Pathology in virally suppressed patients suggests subtle changes that may be reversible.
- Factors driving pathology:
  - Viral factors
  - Host factors
  - Comorbidities
  - Potential ART-mediated adverse effects

- We previously reported:
  - Two first generation HIV protease inhibitors (PIs), ritonavir and saquinavir, led to oxidative stress and induced the unfolded protein response (UPR), with subsequent synaptic damage and neuronal death in vitro.

METHODS

In vitro assessment of antiretroviral drug neurotoxicity
- Primary rat cortical neuronal cultures:
  - 14-16 days in vitro
  - Assessment of neurotoxicity: Immunofluorescent staining for MAP2 (neurons) and DAPI (nuclei) for cell counting
  - Determination of mitochondrial membrane potential: Tetramethylrhodamine methyl ester (TMRM) assay
  - Determination of oxidative stress: CellRox Green live cell imaging with Keyence BZ-X700 digital fluorescence microscope
  - Immunoblotting

RESULTS

Figure 1. Elvitegravir but not dolutegravir is neurotoxic in vitro

A

B

C

D

E

F

Figure 2. Lopinavir but not darunavir is neurotoxic in vitro

A

B

C

D

E

F

Figure 3. Lopinavir induces oxidative stress and mitochondrial damage in vitro

A

B

C

D

E

F

Figure 4. Lopinavir induces the endogenous antioxidant response in primary neurons in vitro

A

B

C

D

E

F

Figure 5. Pharmacological induction of the endogenous antioxidant HO-1 is protective against lopinavir-induced neurotoxicity in vitro

A

B

C

D

E

F

HYPOTHESIS

Neurotoxicity associated with antiretroviral drugs is class-specific

Figure 11. Diagram: Host cell response to viral treatment

IMPLICATIONS

- Differences in the neurotoxicity profiles of antiretroviral drugs not only within classes but also across classes.
- Among integrase inhibitors:
  - Elvitegravir but not dolutegravir is neurotoxic in vitro.
  - Elvitegravir does not induce oxidative stress in neurons in vitro.
- Among protease inhibitors:
  - Lopinavir but not darunavir is neurotoxic in vitro.
  - Lopinavir induces mitochondrial dysfunction and oxidative stress.
- Pharmacological induction of the endogenous antioxidant HO-1 is protective against lopinavir-mediated neuronal death.

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