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NAC Reduces Apoptosis and Telomeres Shortening Subsequent to HIV-1 Exposure in an Astrocytoma Cell Line

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Oxidative stress, involved in HIV-1 disease, plays a key role in the neuropathogenesis of HIV-1 infection. HIV-1 infected cells produce free radicals, involved in the apoptosis of astroglia and neurons. Recent data show that oxidative stress is responsible also of accelerates telomere shortening of human fibroblast in vitro. Our study was focused on the relationship between HIV-1/oxidative stress/astrocytic damage. U373 human astrocytoma cells were directly exposed to X4-using strain HIV-1_{IIIB}, for 1, 3, 5, 10 and 15 days and treated (where requested) with different doses of *N*-acetylcysteine (NAC), compound essential for the synthesis of glutathione (GSH), a cellular antioxidant. Apoptosis was analyzed by FACS analysis, and telomere length, by Quantitative-FISH (Q-FISH). Intracellular GSH and GSSG were determined by high-performance liquid chromatography (HPLC). Statistical analysis was performed by χ^2 test ($p < 0.001$). Incubation of U373 with HIV-1_{IIIB} led to significant induction of cellular apoptosis (1 day: 17%; 3 days: 32%; 5 days: 70%; 10 days: 54%; 15 days: 76%). Apoptosis was reduced of 48% in the presence of 1mM NAC at day 5 after virus exposure ($p < 0.001$). Moreover, NAC improved the GSH/GSSG ratio, a sensitive indicator of oxidative stress that decreased strongly after HIV-1_{IIIB} exposure in U373. Analysis of telomere length showed, in HIV-1 exposed U373, a statistically significant telomere shortening (1 day: 18%; 3 days: 11%; 5 days: 55%), that was completely resumed in U373 NAC-treated. Our results support the role of HIV-1-mediated oxidative stress in astrocytic death, and the importance of antioxidant compounds in preventing these cellular damages. Moreover, indicate that the telomere structure, target for oxidative damage, could be the key sensor of cell apoptosis induced by oxidative stress after HIV infection.

doi:10.1016/j.antiviral.2008.01.093

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A Novel NNRTI Class with Potent Anti-HIV Activity Against NNRTI-resistant Viruses

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Background: Current highly active anti-retroviral therapy (HAART) strategies for HIV infection utilize combinations of at least two classes of anti-retroviral agents. Although HAART has proven to be effective, its benefits can be compromised by the development of drug resistance. For the NNRTIs, many mutations such as K103N cause cross-resistance, rendering this class unavailable for combination therapies in subjects infected with these resistant viruses. Newer NNRTIs, active against the NNRTI-resistant viruses, are urgently needed to expand the NNRTI armamentarium. The characterization of activities against a panel of NNRTI-resistant HIV-1 viruses suggests this NNRTI series has the potential to overcome the most prevalent of these resistant strains.
Methods: Antiviral activities of the NNRTIs were determined using either VSV-g pseudotyped HIV-1 containing wild type (wt) and NNRTI-resistant sequences or clinical HIV-1 isolates containing NNRTI-resistant mutations. Cytotoxicity was evaluated in primary human cells and cell lines. Non-linear regression analysis was used to calculate IC_{50} values.
Results: The NNRTI series comprises potent inhibitors of wt HIV-1 with EC_{50} values of approximately 1 nM and CC_{50} values of >50 μM. The fold changes (FCs) in EC_{50} against the major NNRTI-resistant viruses found in patients failing efavirenz therapy are significantly lower than those of efavirenz. For instance, FCs for compounds in the series against K103N are <1, versus >10 for efavirenz. The FC in activity over wild type virus in a broad panel of NNRTI-resistant mutant viruses is superior to efavirenz and superior or similar to the TMC NNRTIs in development. These compounds are stable in human plasma.
Conclusions: Compounds in this series are potent NNRTIs with a large selectivity index. They are superior to efavirenz against a broad panel of NNRTI resistant viruses. The in vitro characterization of these novel NNRTIs shows strong potential for improved performance over current NNRTIs and warrants further evaluation.

doi:10.1016/j.antiviral.2008.01.094

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A Recombinant, Infectious Human Parainfluenza Virus Type 3 Expressing the Enhanced Green Fluorescent Protein for Use in High Throughput Antiviral Assays

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For some viruses, antiviral assays are quite tedious, either in the duration of the assay or the difficulty of growth in cell culture. The ability to rescue an infectious, RNA virus from a cDNA clone has led to new opportunities for