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Creatine Phosphate Inhibits the Replication of HIV in Macrophages.

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Creatine kinase (CK) and its substrates creatine (Cr) and creatine phosphate (CrP), referred to as the creatine kinase system, are involved in the rapid regeneration of ATP at sites of cellular work. The brain isoform of CK (CKBB) is induced over 100-fold upon the differentiation of monocytes into macrophages, suggesting an important function in these mature cells. T cells do not express detectable levels of CK. To investigate the potential role of the CK system in HIV-infected macrophages, we have synthesized and evaluated the antiviral activity of a series of analogs of both substrates (Cr and CrP). We demonstrate that CrP inhibits the replication of HIV-1 (Bal) in fresh macrophages with an ED_{50} of approximately 1.5 mM. To determine if this activity is also found in HIV-infected T-cells, we evaluated the compound in CEM and MT-2 cells infected with HIV-1 RF and IIIB strains, respectively. CrP did not inhibit replication of HIV in these T cell lines. Previously, analogs of Cr such as cyclocreatine were shown to inhibit replication of several members of the herpesvirus family, both *in vitro* and *in vivo*. The active compounds required uptake and efficient phosphorylation by CK and yielded synthetic phosphagen pools that generated ATP at reduced rates relative to the natural phosphagen. The surprising finding of the anti-HIV activity of CrP, which is a charged molecule that is poorly taken up by cells, suggests an extracellular mechanism. We propose that CrP and potentially its analogs represent a new class of anti-HIV agents that work through a distinct mechanism of action from that of the Cr analogs reported previously.

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Zidovudine (AZT) Treatment Of Liver Cells Causes Accumulation Of Intracellular Lipid Droplets, And Phosphorylated Zidovudine Intracellularly Increases Lactate In Medium, And Inhibits Mitochondrial Dna Polymerase-γ.
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Zidovudine (AZT, 3'-azido-3'-deoxythymidine) causes hepatotoxicity with steatosis and lactic acidosis. We hypothesized that AZT hepatic toxicity was caused by accumulation of phosphorylated AZT derivatives in hepatocytes, by AZT triphosphate (AZTTP) inhibition of mitochondrial DNA polymerase-γ (DNA pol-γ), and by resultant alterations in oxidative metabolism with increased anaerobic metabolism. We created a model of AZT steatosis using HepG2 cells treated with AZT (0-500 μM; 7-28 days). Lactate content in the medium was determined. Intracellular AZT phosphorylation was assessed by defining the abundance of phosphorylated AZT derivatives in HepG2 homogenates. Inhibitory concentrations (IC_{50}) of AZTTP, AZT monophosphate (AZTMP), and AZT were defined with DNA pol-γ. After 14 days AZT treatment, AZTMP was the most abundant phosphorylated derivative with much lower AZT diphosphate (AZTDP) and AZTTP. In parallel, intracellular vesicular fat was visible microscopically (100 μM AZT). Lactate content in medium (≥100 μM AZT; 14 days) rose to twice that found in controls. AZTTP IC_{50} with DNA pol-γ was 8 μM using poly(rA)•oligo(dT). Neither AZT nor AZTMP significantly inhibited DNA pol-γ. AZT treatment caused phosphorylated AZT metabolites to accumulate in liver cells with vesicular steatosis. Lactate accumulated in the medium. AZTTP inhibited hepatic DNA pol-γ. Inhibition of DNA pol-γ by AZTTP may be pathogenetically linked to AZT hepatic steatosis in ways that that are analogous to those seen in other tissues.