Inhibitors of Herpes Simplex Virus Thymidine Kinase Synthesis and Biological Properties

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Herpes simplex virus (HSV) encoded thymidine kinase (TK) has been implicated in the establishment and development of HSV infections in vivo. TK^- mutants of this virus are known to have a modified propensity for spread within the nervous system and it follows that inhibition of this enzyme may influence the course of infection, especially aspects of latency. Inhibitors of HSV-TK might be expected to display antiviral activity in appropriate models but potent and selective inhibitors of this enzyme have not been described hitherto. We have designed and synthesised a range of novel nucleoside derivatives as product analogues that are potent (IC_{50} 10^{-9}M) and highly selective inhibitors of HSV-TK. The synthesis, structure-activity relationships and some biological properties of these compounds will be discussed.

Inhibition of HIV-1 and Simian Immunodeficiency Virus (SIV) Reverse Transcriptases by the 5'-Triphosphates of 3'-Azido-2',3'-dideoxyuridine (CS-87), 3'-Azido-3'-deoxythymidine (AZT), and 3'-Azido-2',3'-dideoxy-5-ethyluridine (CS-85). B. F. H. Eriksson[1*], R. F. Schinazi[1], and C. K. Chu[2]. Veterans Administration Med. Ctr., and Emory University School of Medicine, Dept. of Pediatrics, Atlanta, Ga.[1], and University of Georgia, Athens, Ga[2].

Several 2',3'-dideoxynucleosides have been shown to be potent and preferential inhibitors of human immunodeficiency virus (HIV-1) replication *in vitro*. The major target enzyme affected is thought to be the HIV-1 reverse transcriptase (RT). RTs from HIV-1 (LAV)- and SIV (SMM)-infected cultures of human peripheral blood mononuclear cells were partially purified, and the effects of the 5'-triphosphates of CS-87, AZT, and CS-85 were investigated. All three triphosphates inhibited HIV-1 and SIV RTs in a competitive manner with respect to the normal substrate dTTP. The triphosphates of AZT and CS-87 were about equally potent against HIV-1 and SIV RTs, whereas CS-85-TP was about 10 times less potent. The apparent K_i-values of AZT-TP, CS-87-TP, and CS-85-TP using HIV-1 RT were 4.0, 5.9, and 50 nM, respectively, in $(rA)_n \cdot (dT)_{12-18}$-directed reactions using 1 μM dTTP. Corresponding K_i-values using SIV RT in similar reactions were 5.0, 7.5, and 45 nM, respectively. The K_m for dTTP was determined to be about 0.5 μM and 1.5 μM for HIV-1 and SIV RTs, respectively, showing that the triphosphates had a 30-300 times higher affinity for the enzymes than dTTP. Cellular DNA polymerase α activity was reduced by 50% at 20-30 μM AZT-TP or CS-87-TP and at 375 μM CS-85-TP in reactions directed by activated calf thymus DNA, when dTTP was maintained at 1 μM. These results indicate that AZT-TP and CS-87-TP are equally effective and selective inhibitors of HIV-1 and SIV RTs. Although CS-85-TP was about 10 times less potent, its selectivity was similar to the other antiviral nucleotides. *(Supported by USPHS grant 44094, and the Veterans Administration)*