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Potentiation of the Anti-HIV Activity of ddAdo by Coformycin, EHNA and deaza-EHNA Derivatives. P. La Colla^, G. Cristalli*, P. Franchetti*, M. Grifantini*, E. Tramontano^, M.E. Marongiu^ and A. Pani^. Depts. of ^Biologia Sperimentale, Universita' di Cagliari and *Scienze Chimiche, Universita' di Camerino. Italy.

2',3'-dideoxyadenosine (ddAdo) and 2',3'-dideoxyinosine (ddIno) are potent and selective inhibitors of HIV-1 multiplication. Equipotent in terms of antiviral activity, both compounds selectively inhibit the HIV-1 reverse transcriptase upon conversion into ddATP. Contrary to other ADA-sensitive compounds, such as 3'-deoxyadenosine (Cordycepin) or 9-B-D-xylofuranosyl-adenine (ara-A), the antiviral activity of ddAdo is not potentiated by 2'-deoxycoformycin (2-dCF) (Cooney et al., Biochem. Pharmacol. 36, 3797 (1987)). Therefore, we investigated the anti-HIV effect of ddAdo in combination with other ADA-inhibitors, namely Coformycin (CF), 9-(eritro-2-hydroxy-3-nonil)adenine (EHNA) and some 3-deaza-EHNA derivatives. All these ADA inhibitors potentiated the anti-HIV activity of ddAdo but not that of ddIno. Potentiation was obtained with concentrations of CF and EHNA up to >12,500 and 250 times lower than the respective maximum non toxic doses. In combination with CF or EHNA, ddAdo inhibited the HIV-1 multiplication at concentrations up to ten times lower than those required to obtain the same degree of inhibition when it was used alone. Potentiation of the anti-HIV-1 activity of ddAdo by CF or EHNA was not mediated by an increase in cytotoxicity.

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Stilbene disulfonic acids: CD4 antagonists that block human immunodeficiency virus Type-1 growth at multiple stages of the virus life cycle. A.D. Cardin, P.L. Smith, L. Hyde+, D.T. Blankenship, T.L. Bowlin, K. Schroeder, D.L. Taylor+ and A.S. Tyms+. Marion Merrell Dow Research Institute, Cincinnati, OH 45215, and the Medical Research Council Collaborative Center, London, UK+

The stilbene disulfonic acid DIDS (4,4'-diisothiocyanatostilbene-2,2'-disulfonic acid) and related analogs inhibit CD3-T cell antigen receptor-stimulated Ca^{+2} influx in human T lymphocytes (Rosoff et al. J. Biol. Chem. 263, 19535-19540, 1988). We report that DIDS binds the variable-1 (V_1) immunoglobulin-like domain of membrane-associated and soluble recombinant CD4 (sCD4). This interaction blocks the binding of the anti-CD4 monoclonal antibody OKT4A and the HIV-1 envelope glycoprotein gp120. DIDS inhibited HIV-1 growth in CD4+ JM cells with an IC_{50} (~30 μM) similar to that required to block gp120 binding (~20 μM) to membrane-associated CD4 on JM cells. Addition of DIDS to cells at 43 h post-infection (p.i.), at a time when syncytia were established, cleared the cultures of syncytia by 68 h p.i. Preincubation of uninfected CD4+ C8166 cells with DIDS blocked their CD4-dependent fusion with chronically infected H9 cells. DIDS covalently modified lysine-90 of sCD4 and abolished the gp120 binding and antiviral properties of the recombinant protein. That the stilbene disulfonic acids bind the V_1 domain of CD4 and block multiple CD4-dependent events associated with acute and established HIV-1 infections demonstrates their potential use as antiviral agents.