11

Antiviral Properties of BMS 182,193, an Aminoalcohol Inhibitor of HIV Protease
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Human immunodeficiency virus (HIV) encodes for a protease which cleaves viral structural proteins. It is essential for production of infectious virus and therefore represents an important target for antiviral therapy. A series of aminoalcohol inhibitors were identified using an in vitro peptide cleavage assay. The compound BMS 182,193 protected cells against acute HIV-1 and HIV-2 infections with IC_{50}s of 0.06 μM to 0.33 μM, respectively and 50% cytotoxic concentrations of 5-10 μM. BMS 182,193 had similar antiviral activity against the replication of HIV-1 IIIB in peripheral blood mononuclear cells. In a time of addition assay, BMS 182,193 could be added as late as 26 hours after infection and still retain activity. To directly show that the culture efficacy of BMS 182,193 was due to inhibition of proteolytic cleavage, chronically infected 8E5 cells were treated with compound. Levels of HIV gag precursor (p55) and its processed protein (p24) in cell lysates were determined by Western Blot analysis. Results indicated that BMS 182,193 blocked the processing of p55 in a dose dependent manner (IC_{50}s of 0.4 μM). To examine the reversibility of a related aminoalcohol inhibitor, HIV-1 RF/CEM-SS cells were treated with drug and virions purified from culture medium. Incubation of virion particles in drug-free medium indicated that inhibition of p55 proteolysis was slowly reversible. The selective inhibitory activities of this compound against both acute and chronic HIV infections warrant its further development.

12

Comparison of Anti-HSV Activity and Metabolism of Acyclic Nucleotide Analogs.
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The phosphonate compounds HPMPC and PMEA have potent anti-HSV and anti-HIV activity and are currently undergoing clinical trials for the treatment of CMV and HIV infections, respectively. The anti-HSV activity and metabolism of the phosphonates and their derivatives were studied in vitro. HPMPC, HPMPA and PMEA inhibited HSV-1 selectively in Vero cells. Ninety percent inhibition of infectious virus yield was achieved at concentration of 1, 10 and 30 μM, respectively. Time of addition experiments showed that the purine phosphonate analogs inhibited HSV-1 infection primarily with continuous drug exposure. By contrast, HPMPC and its prodrug cyclic HPMPC were equally effective at t = o and in pretreated Vero cells infected with virus in drug-free medium. This differential effect of the purine and pyrimidine phosphonate analogs was due, at least in part, to differences in the metabolism of these analogs. Thus, with PMEA the major metabolite formed was the diphosphorylated derivative $PMEA_{pp}$ which showed a decay time (t ½) of 5.5 h; in contrast, HPMPC converted to $HPMPC_{pp}$ and a phosphodiester metabolite ($HPMPC_p$ choline). Rate of removal of $HPMPC_{pp}$ and its liponucleotide derivative was extremely slow with t½ = 43, and 87 h, respectively. These results demonstrate that HPMPC metabolites have a unique stability in Vero cells and thus may permit maintenance of effective level of drug with infrequent administration.