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Inhibition of HBV Polymerase by Nucleotide Analogs: Differential Activity of Enantiomers. MG Davis[1], SL Smith[1], JE Wilson[1], A Aulabaugh[1], SM Daluge[2],NA VanDraanen[3],FL Boyd[3], WH Miller[3], and JM Cullen[4].[1]Division of Virology, [2]Division of Organic Chemistry, [3]Division of Experimental Therapy, Burroughs Wellcome Co., Research Triangle Park, NC 27709, USA, [4]Dept. of Microbiology, Parasitology and Pathology, College of Veterinary Medicine, NCSU, Raleigh, NC 27514, USA.

Polymerase activity was assayed in HBV viral and core particles isolated from chronic producer lines (2.2.15 and HB611) and in WHV particles in serum collected from a chronically infected woodchuck. The particle-associated activity, which was found to be limited to incorporation of only a few nucleotides, was inhibited by triphosphates of nucleoside analogs. The L and D enantiomers of 2',3'-dideoxynucleotides ddCTP and ddTTP, as well as the triphosphates of the L and D enantiomers of the antiviral compounds d4T, carbovir, 3TC and FTC (cis-5-fluoro-1-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine) were compared for the ability to inhibit incorporation of natural nucleoside triphosphates into the viral DNA. All of these compounds are obligate chain-terminating nucleotide analogs. The triphosphates were previously found to be substrates for HIV reverse transcriptase; the D enantiomers of some pairs were preferred as substrates. In contrast, for all compounds, the L enantiomer was the more potent inhibitor of incorporation into HBV DNA; the concentration required to inhibit the incorporation of the natural β-D-ribose deoxynucleoside triphosphate by 50% was five- to one-hundred-fold lower than the concentration of the D enantiomer required for the same inhibitory effect. This preference for the L enantiomers was observed for both RNA-directed synthesis in core particles and DNA-directed synthesis in viral particles. In some cases, the concentration of inhibitory nucleotide was five to one hundred-fold lower than the concentration of the normal labeled nucleotide. The observed antiviral effect of these compounds is limited chiefly by their phosphorylation in cells, which is sufficient for FTC and 3TC, but not for other L nucleosides.

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Novel Ether Lipid Analogs of Platelet Activating Factor with Anti-Hepatitis B Virus Activity. L. Kucera, C. Fowler, N. Iyer, and C. Whang, Bowman Gray School of Medicine of Wake Forest University, Winston-Salem, NC 27157, and S. Morris-Natschke, K. Ishaq, and C. Piantadosi, The University of North Carolina, Chapel Hill, NC 27599, U.S.A.

Ether lipid (EL) analogs of platelet activating factor (PAF) are membrane interactive compounds that inhibit infectious human immunodeficiency virus multiplication. Experiments were done to determine effects of EL analogs on hepatitis B virus (HBV) replication using human hepatoblastoma (Hep G2) cells transfected with plasmid DNA containing tandem copies of the HBV genome. These cells constitutively replicate HBV particles. Hep G2 cells were treated with various concentrations of EL to determine the toxic cell concentration $_{50}$ ($TC_{50}$) by neutral red dye uptake or the inhibitory concentration $_{50}$ ($IC_{50}$) for HBV replication by ELISA. Results indicated that compounds CP128, CP50, CP23, and lyso PAF had $TC_{50}$'s of 61.7, 62, $<3$ and $>100$ $\mu$M and $IC_{50}$'s of 15.6, 8.9, 3.1, and $>20\mu$M, respectively. These data indicate that some EL have selective anti-HBV activity. Continuous treatment of infected cells with EL for 2 to 3 days is required to achieve maximum anti-HBV activity. The T½ for antiviral activity is more than 4 days. EL inhibit HBV induced DNA, core antigen (HBcAg) and "e" antigen (HBeAg) syntheses. In contrast, EL had no detectable effect on RNA or surface antigen (HBsAg) syntheses. In summary, the antiviral EL are most likely inhibiting the assembly of HBV nucleocapsids and packaging of viral pregenomic RNA.