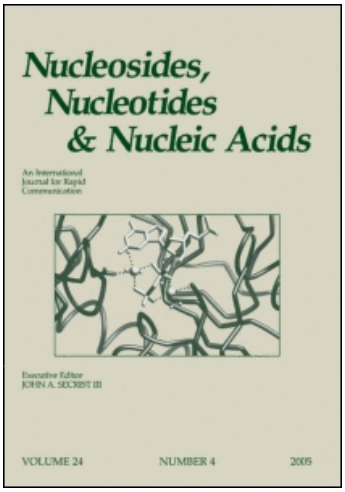

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Comparison of Anti-HBV Activity of β-D- and β-L-ddA-5'Monophosphate Prodrugs and Effectiveness in Combination with Lamivudine

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COMPARISON OF ANTI-HBV ACTIVITY OF β-D- AND β-L-DDA-5'MONOPHOSPHATE PRODRUGS AND EFFECTIVENESS IN COMBINATION WITH LAMIVUDINE.

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ABSTRACT: We have investigated the effects of several β-D-ddA 5'-monophospate (β-D-ddAMP), and their corresponding β-L-enantiomers prodrugs against HBV replication. All ddAMP prodrugs inhibited HBV replication in a dose-dependent manner.

Introduction

Recently, several unnatural configured L-nucleosides with potent anti-HBV activity and low toxicity compared with their natural D-enantiomers have been developed[1] Furthermore, we have described the synthesis and biological activity of several prodrugs of nucleoside 5'-monophosphate[2]. We report the in vitro properties of β-D and β-L-2',3'-ddAMP and the combination study of the most selective β-L-ddAMP prodrug with lamivudine.

Materials and methods

Antiviral Assay. The 2.2.15 cell line was cultured as previously[1]. The effects of drug combinations were analyzed using the ComboStat software program. *Woodchuck hepatitis B DNA polymerase assay.* In vitro assays were performed using sucrose gradient centrifugation of virus particles from WHV positive serum, generously provided by B. Tennant (Cornell University, Ithaca, N.Y) as described[1].

Result and conclusion

The ddAMP prodrugs proved to be more potent than their parental nucleoside. However, β-L-ddAMP prodrugs were more potent with EC_{50}'s values 2 to 5-fold lower than their corresponding β-D-enantiomers. Among all prodrugs, β-L-ddAMP-bis(methylSATE) and β-L-ddAMP-bis(tbutylSATE) were found to be the most active with EC_{50}'s of 0.08 and 0.1 μM, respectively. Moreover, the anti-HBV activity of these compounds was confirmed in primary duck hepatocyte culture infected with duck hepatitis B virus. β-L-ddAMP prodrugs were also found to be less cytotoxic than their corresponding β-D-ddAMP derivatives. Clonogenic in vitro assays revealed that β-D-ddA, β-L-ddA and β-L-ddAMP prodrugs did not inhibit CFU-GM and BFU-E cultures up to a concentration of 10 μM with the exception of β-L-ddAMP 5'-bis(tbutylSATE) which exhibited a CC_{50} value of 6 μM in CFU-GM cultures. β-L-ddATP was found to be a more potent inhibitor of WHV DNA polymerase than its natural corresponding β-D-ddATP Moreover, the inhibitory effect of β-L-ddATP toward viral polymerases was selective since β-L-ddATP did not inhibit in vitro DNA polymerase α or β up to a concentration of 100 μM.

Finally, the combination of 3TC plus β-L-ddAMP-bis(tbutyl-SATE) at molar ratio of 1:5 and 1:2 showed synergistic effects at different levels of inhibition, with combination index values of 0.21-0.26 and 0.10-0.35, respectively. The doses of 3TC and β-L-ddAMP-bis(tbutyl-SATE) required to achieve the same degree of inhibition by monotherapy could be reduced from 4 to 10-fold in a synergistic combination.

In conclusion, our results indicate that β-L-ddAMP prodrugs are potent and selective inhibitors against HBV replication *in vitro* and that the synergistic effect of β-L-ddAMP-bis(tbutylSATE) in combination with 3TC supports their further developments.

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