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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'-monophosphate (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 developed¹. Furthermore, we have described the synthesis and biological activity of several prodrugs of nucleoside 5'-monophosphate². 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 previously¹. 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 described¹.

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 μ M, 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 μ M with the exception of β -L-ddAMP 5'-bis(tbutylSATE) which exhibited a CC_{50} value of 6 μ M 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 μ M.

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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