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Inhibition of Duck Hepatitis B Virus DNA Polymerase by the Triphosphate of Fialuridine. A. J. Schilke, K. A. Staschke, and J. M. Colacino*. Lilly Research Laboratories, Indianapolis, Indiana, USA.

Fialuridine (FIAU) is a potent inhibitor of hepatitis B virus both in vitro and in the woodchuck model of chronic HBV infection. The selective in vitro activity is due, at least in part, to the direct inhibition of the viral DNA polymerase by the triphosphate of FIAU (FIAUTP). In an endogenous DNA polymerase assay using concentrated duck hepatitis B virus particles as the polymerase source and gel electrophoresis of the resulting ^{32}P-labeled 3.2 Kbp viral DNA product, FIAUTP inhibits the incorporation of ^{32}P-TTP in a dose dependent manner. At 0.038 μM, the formation of radiolabeled DNA was reduced by 50%. In comparison, phosphonoacetic acid and dideoxycytidine triphosphate, known inhibitors of the enzyme, showed IC_{50}'s of 1.0 μM and 0.56 μM, respectively. FIAUTP could not replace any nucleoside triphosphate omitted from the reaction indicating that this nucleotide analog does not act as an alternative substrate, but rather as an inhibitor of the viral DNA polymerase.

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Effects of IFNα on HBV Gene Expression in Transgenic Mice

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While there is a clear epidemiologic association between hepatitis B virus (HBV) infection and the development of hepatocellular carcinoma (HCC) in men, the underlying mechanism of etiology remains obscure. There has been suggestion that continuous liver cell injury and regeneration, which accompany chronic hepatitis induced by HBV, may facilitate selection of random mutations that confer an unlimited growth potential. Alternatively, it has been speculated that random integration of HBV may lead to downstream activation of specific growth-promoting genes. In either case, HBV would only "indirectly" contribute to the development of liver cancer. Our recent observation that introduction of a single HBV transactivator gene (HBx) into transgenic mice was sufficient to induce progressive changes in the liver, beginning with altered foci made up of highly vacuolated cells, to benign adenomas, and ending with malignant carcinomas, strongly argues for a "direct" role for HBV in the development of HCC. Since our HBx gene is under the regulation of its own transcriptional control element which has been implicated to be the target for the action of interferon-α (IFNα), we sought to determine whether the recombinant IFNα B/D hybrid will be efficacious in turning off HBx gene expression in our transgenic mice. The results we obtained are exceedingly encouraging.