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Mechanism of Action of (±)-(1α,2β,3α)-9-[2,3-Bis(hydroxymethyl)-cyclobutyl]-guanine (BHCG). B. J. Terry, K. E. Mazina, M. L. Haffey, and A. K. Field. The Squibb Institute for Medical Research, Princeton, New Jersey 084543-4000 USA.

(±)-(1α,2β,3α)-9-[2,3-*bis*(hydroxymethyl)cyclobutyl]guanine (BHCG) is a nucleoside analog with potent *in vitro* activity against herpesviruses. The efficacy of BHCG against herpesvirus infections in mice confirms the interest in this compound as an antiviral drug. BHCG triphosphate was enzymatically synthesized with thymidine kinase, GMP kinase, and nucleoside-5'-disphosphate kinase. The triphosphate is a competitive inhibitor with respect to dGTP incorporation into DNA by both HSV-1 DNA polymerase and HeLa DNA polymerase α. BHCG-TP is an uncompetitive inhibitor with respect to dATP and dTTP incorporation into DNA. BHCG-TP is a selective inhibitor of purified HSV-1 DNA polymerase (K_i = 0.012 μM) compared to HeLa DNA polymerase α (K_i = 2.2 μM). BHCG-TP was examined for its ability to be incorporated into, and excised from, a synthetic (oligo:primer) DNA template in comparison to dGTP, acyclovir (ACV) triphosphate and ganciclovir (GCV) triphosphate. All four triphosphates studied were incorporated into the DNA template. Compared to dGTP, only limited extension of the primer occurred following incorporation of BHCG-TP or GCV-TP and no extension was seen following ACV-TP incorporation. BHCG monophosphate (MP) could be removed from the 3' terminus of the primer less readily than dGMP but far better than either ACV-MP or GCV-MP by the 3'-5' exonuclease activity of the HSV-1 DNA polymerase.

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Design of herpesvirus-specific glycosylation inhibitors. R. Datema, Bristol-Myers Squibb Company, 5 Research Parkway, Wallingford, CT 06492-7660, U.S.A.; S. Olofsson, University of Goteborg, Goteborg, Sweden; D. Shugar, Academy of Sciences, Warsaw, Poland; C. Hirschberg, University of Massachusetts, Worcester, MA, U.S.A.

Peripheral (terminal) carbohydrate residues of protein-linked oligosaccharides do not play a role in the formation of infectious virus particles in all systems investigated to date. However, recent results indicate that interference with terminal glycosylation can increase the availability of viral glycoproteins for immune responses. To study these effects in vivo, virus specific inhibitors of terminal glycosylation are needed. We have described a strategy to obtain HSV-specific glycosylation inhibitors. This involves selective phosphorylation in infected cells of a nucleoside analog to a 5'-monophosphate, which inhibits translocation of sugar nucleotides from the cytoplasm into the Golgi compartment where terminal glycosylation occurs (Virology (1988), 160, 440-50). We tested several HSV-TK-activated nucleosides for their potential to enhance the antigenicity of the HSV-1 glycoprotein gC-1, when added after the initiation of HSV-DNA synthesis. Of these, the analog 5-propyl-2'-deoxyuridine (PdU) alters terminal glycosylation resulting in (a) a decrease in the proportion of highly branched N-linked oligosaccharides, (b) a decrease in terminal galactosylation and sialylation, (c) an increase in the availability of gC-1 for polyclonal neutralizing antibodies. The effect is strictly TK-dependent and is not caused by an increased gC-1 synthesis, etc. Further, PdU-5'MP inhibits the pyrimidine sugar nucleotide translocation. Hence, this strategy offers the possibility of designing herpesvirus specific glycosylation inhibitors.