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Elucidation of the Mechanism Responsible for the Synergistic Effects of DL-Homocysteine (Hcy) on the Anti-Vaccinia Virus Effects of the S-Adenosylhomocysteine (AdoHcy) Hydrolase Inhibitor 9-(Trans-2', Trans-3'-Dihydroxycyclopent-4'-Enyl)-Adenine (1). M. Hasobe, J. G. McKee, H. Ishii and R. T. Borchardt. Department of Pharmaceutical Chemistry, University of Kansas, Lawrence KS, 66045, U.S.A.

Compound 1, an analog of neplanocin A, is a specific inhibitor of cellular AdoHcy hydrolase (M. Hasobe et al., Fed. Proc. **46**:93, 1987) and an anti-vaccinia virus agent which selectively inhibits viral replication over cell growth in murine L929 cells (M. Hasobe et al., Antimicrob. Agents Chemother. **31**:1849, 1987). This selectivity has been suggested to depend upon the degree to which the intracellular AdoHcy is elevated. (M. Hasobe et al., J. Pharm. Sci. **76**(11):S40, 1987). Anti-vaccinia virus activity of compound 1 was correlated to the elevation of AdoHcy which results from inhibition (70-80%) of AdoHcy hydrolase in L929 cells. Measurement of the intracellular content of Hcy in cells treated with 1 showed that the elevation in intracellular AdoHcy was paralleled by an elevation in intracellular Hcy. When exogenous Hcy and 1 were added to L929 cells infected with vaccinia virus, synergistic effects on the antiviral activity and the accumulation of intracellular AdoHcy were observed. In cells treated with 1 (0.1 μM) and Hcy (3 mM) for 1 hour and then pulse labeled with [^{35}S]methionine and [^{3}H]adenosine, the [^{3}H]/[^{35}S] ratio in AdoHcy showed stimulation of AdoHcy formation results from reaction of adenosine and Hcy which was probably catalyzed by the residual activity (10-20%) of AdoHcy hydrolase. These observations suggest that the antiviral mechanism of compound 1, both alone and in combination with Hcy, depends on the elevation of intracellular AdoHcy. (Supported by grants from NIGMS and Glaxo Inc)

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The Comparative Antiviral Action of Ribavirin Against Selected Bunyaviruses. J.J. Kirsi and P.G. Canonico. U.S. Army Medical Research Institute of Infectious Diseases, Fort Detrick, Frederick, Maryland, 21701-5011, U.S.A.

The antiviral effects of three related carboxamides, ribavirin, tiazofurin and selenazofurin, have been tested in Vero-76 cells against selected bunyaviruses of the California serogroup: California encephalitis, snowshoe hare and LaCrosse. The overall antiviral effects of the compounds against these viruses are very similar. When the ED_{50} of the compound was measured, selenazofurin gave the best results (<10μM) and tiazofurin and ribavirin were closely equal to each other (>250μM). In contrast, when ED_{90} was used as the criterion, only ribavirin attained this inhibitory level at concentrations below observable cytotoxicity. Hence, selenazofurin and tiazofurin are considered to be relatively ineffective against these viruses. However, in cytotoxicity studies, the contact-inhibited Vero cells tolerated ~ 1000-fold greater quantities of ribavirin than actively dividing cells. In actively dividing cells, the cellular ED_{50} of ribavirin was less than 100μM. The addition of extraneous guanosine abolished the antiviral action of ribavirin, as did the postponement of treatment for more than 6 hr. Pretreatment of cells with ribavirin did not significantly improve its effectiveness. These observations suggest that the inhibition of dividing Vero-76 cells occurs at concentrations lower than those required for the inhibition of the bunyaviruses tested. Thus, in this assay system, the specific antiviral mode of action and cytotoxic effects of ribavirin cannot be unambiguously separated.