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NUCLEOTIDE ANALOGUE-9(4-HYDROPHOSPHORYL-2-OXABUTYL)-GUANINE; RIBAVIRINE (ICN) AND TROMANTADINE (VIRU-MERTZ) AS EFFECTIVE INHIBITORS TK^- AND PAA^R STRAINS OF THE HSV-1 IN VITRO.

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We demonstrated that new nucleotide analogue 9-(4-hydrophosphoryl-2-oxabutyl)-guanine (1) (synthesized in the Institute of Molecular Biology, Moscow) inhibits effectively HSV-1 reproduction in Vero cells. The action of (1) on HSV-1 is highly selective. (1) is twelve times less toxic than acyclovir (2). ID_{50} for (2) is 0,28 μg/ml, for (1) - 4,0 μg/ml; (2) is not effective with respect to HSV-1(TK^-) ID_{50}-6,8 μg/ml; (1) preserve substantial activity - ID_{50}-4,3 μg/ml, ID_{95}- 10,6 μg/ml - (1); in this concentration (1) inhibits reproduction HSV-1(TK^-) by 3,8 lg $TCID_{50}$; (1) inhibits reproduction HSV-1 PAA^R-ID_{50} - 4,6 μg/ml; (2) - ID_{50}- 1,25 μg/ml. In our opinion (1) does not need activation by means of thymidinkinase of HSV-1. Therefore it is active with respect to HSV-1TK^-. (1) and other nucleotide analogues is a new group of antiherpetic drugs. Ribavirin (3) and Tromantadine-N1-adamantyl-N-2 (dimethylamino ethoxy) acetamide (4) inhibit equally HSV-1 reproduction and strains TK^- and PAA^R; (3)-ID_{50}-21 μg/ml, (4)-ID_{50}-60 μg/ml. The combinations 3 and 4 result in synergistic effect; antiviral effect is selective. In the combination the concentration of (3) 5,5 is lowered; (4) 4 times is lowered.

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HSV-1 Polymerase Activity is Stimulated <u>in vitro</u> by Complex Formation with UL42, its Accessory Protein.

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The DNA-dependent DNA polymerase (Pol) of herpes simplex virus type 1 exists in infected cells as a stable complex with UL42, a virally-encoded accessory protein which has been found to copurify with Pol from infected cells. UL42 is an essential gene for virus replication and mutant viruses which are defective in UL42 expression fail to replicate their DNA following infection of tissue culture cells. The molecular interaction of Pol with UL42 is therefore an attractive novel antiviral target. Pol and UL42 have been overexpressed in recombinant baculovirus vectors and the purified proteins utilized in <u>in vitro</u> assays. Recombinant Pol combined to form a stable complex with purified UL42 <u>in vitro</u> and exhibited increased synthetic activity on a number of DNA template-primers. The UL42-mediated stimulation of Pol activity was shown to result, at least in part, from higher processivity of the Pol/UL42 complex. We have utilized a sensitive assay to measure the stimulation of Pol activity by purified UL42 <u>in vitro</u>.