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Interactions of reproductive ability of herpes simplex virus (HSV) type I and its variants, resistant to acyclovir (ACV) and phosphonoacetic acid (PAA) with proliferative activity of VERO cells. Nikolaeva S.N., Boreko E.I., Erokhina I.R., Votyakov V.I. Byelorussian Research Institute for Epidemiology and Microbiology, Minsk, Republic of Belarus.

Proliferative activity of VERO cells infected with HSV and its variants, resistant to chemical drugs, has been previously investigated by us (Proceed.7th Int. Conf. Antiviral Res.,1994). Studies on virus reproductive ability under similar conditions permitted us to establish its imperfect correspondence to the level of cell mitotic activity. Thus, while HSV variants-infected cells, that were sensitive and resistant to ACV and PAA effect, demonstrated similar virus yield, mitosis number of cells, infected with resistant strain, was lower in comparison with those,infected with primary HSV. In case ACV 0,10 and PAA 20 mkg/ml were added correspondingly to cell supportive medium, infected with ACV and PAA - resistant HSV variants, the increase in virus yield and cell mytotic activity was determined. If the drug, to which the given variant isn`t resistant, was added, the decrease in virus yield was noted with simultaneous increase in mitosis number. Our findings allow us to assume the presence of peculiar interactions of virus-induced process with cell proliferative activity in the period of formation of inhibitor-resistant virus variants.

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Antiviral activity of nucleoside derivatives against acyclovir-resistant mutants of herpes simplex virus type 1

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To understand drug mode of action by studying cross resistance and to investigate the possibility mapping viruses, especially viral thymidine kinase gene, according to antiviral spectrum of drug-resistance mutants. We have previously characterized the laboratorially derived 9 acyclovir (ACV)-resistant mutants of herpes simplex virus type 1 (HSV-1) strain F. Each mutant showed different drug-resistance spectrum to nucleoside analogues. We have attempted to isolate new drug-resistant mutants of HSV-1 strain MacIntyre which shows higher EC_{50} values than those of strain F. Four ACV-resistant mutants were isolated from 4 plaques appeared on Vero cell monolayers in the presence of high dose of acyclovir and 3 times plaque purified. All of them showed about 20-fold increased resistance to ACV and no thymidine kinase activity. Their drug-sensitivity to Foscarnet and phosphoacetic acid was similar to that of the parental type. To examine cross resistance, antiviral activity of various nucleoside derivatives was measured by using CPE inhibition assay in Vero cell culture system. Like the mutants of strain F, each one showed different drug-sensitivity to certain compounds which are specific to only one of 4 mutants. For example, the mutant MIR-3 showed extremely higher resistance to Ganciclovir. From these results of relative drug sensitivity it is assumed that the mutated sites on viral genome, most probably on TK gene, are not identical and that a change on specific site gives influence on antiviral activity of several compounds. For further information DNA sequences of the mutated regions are required.