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Correction of Herpes Simplex Virus-Induced Dyslipidemia by Antiviral Chemical Preparations

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We studied the influence of herpes simplex virus (HSV) on lipid homeostasis and found out possible correction of the detected disturbances by antiherpetic preparations. In conditions of acute HSV infection of rabbits followed by generalization of pathologic process we detected dyslipidemia (DL), characterised by increase in contents of total cholesterol, lipoproteins of low and very low density and triglycerides in the absence of expressed changes in concentration of high density lipoprotein. Similar DL was also detected in patients with ophtalmoherpes. HSV infection of smooth muscle cell culture was accompanied by increased accumulation of free lipids in cells. The use of known antiherpetic preparations, furavir and acycloguanosine led to correction of lipid spectrum of infected animals and to normalization of intracellular lipid contents. Disturbances in lipid metabolism are the key point in the pathogenesis of several cardiovascular diseases. The ability of chemical antivirals to correct HSV-induced DL opens new aspects of their therapeutic effect related to inhibition of the virus, which is a risk factor in formation of such diseases. The obtained data extend our knowledge about pathogenesis of herpetic infection related with the changes of blood and vessel state.

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Selection of the Acetal 2-Amino-9-[3-(isopropoxymethoxy)propoxy]purine (BRL 55792) as an Oral Prodrug of the Anti-herpesvirus Agent 9-(3-Hydroxypropoxy)guanine (BRL 44385)

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9-(3-Hydroxypropoxy)guanine (BRL 44385), a novel acyclonucleoside in which the acyclic substituent is attached to N-9 of the purine via a N-O bond, is a potent and selective inhibitor of HSV-1, HSV-2, VZV and EBV. Like other acyclic analogues of guanosine it is, however, only poorly absorbed after oral administration to animals. A number of ether and acetal derivatives of BRL 44385 and its 2-aminopurine congener (BRL 46720) were synthesized and the bioavailability of BRL 44385 after their oral administration to mice was determined. High (90μM at 0.25h after dosing) and prolonged (1μM at 3h after dosing) concentrations of BRL 44385 in the blood were obtained after a single 0.2mmol/kg dose of 2-amino-9-[3-(isopropoxymethoxy)propoxy]purine (BRL 55792) and this acetal derivative was selected for further evaluation in other species. In rats, the bioavailability of BRL 44385 after oral administration of a single 0.2mmol/kg dose of BRL 55792 was approximately 30%, as compared with <0.2% after administration of BRL 44385 itself. In squirrel monkeys, the bioavailability of BRL 44385 obtained after oral administration of a single 0.11mmol/kg dose of BRL 55792 was about 3-fold higher than that obtained with BRL 44385 (AUC values of 43 and 13μMh, respectively). Orally administered BRL 55792 was shown to be at least 3-fold more potent than BRL 44385 in reduction of lesion severity in a cutaneous HSV-1 infection in ear pinnae of mice. Twice daily doses of 0.066mmol/kg of BRL 55792 administered for 4 days commencing 1h after infection reduced overall lesion severity by 71%, whereas BRL 44385 given in the same way at 0.2mmol/kg afforded 63% reduction. These data demonstrate that the increased bioavailability of BRL 44385 after oral administration of BRL 55792 results in increased antiviral efficacy *in vivo* and confirm the potential of BRL 55792 as an oral prodrug of BRL 44385.