65

Marked Inhibition of Human Immunodeficiency Virus Type 1 and Type 2 by α-(1-3)- and α-(1-6)-D-mannose-specific plant lectins

J. Balzarini[1], D. Schols[1], E. Van Damme[2], W. Peumans[2] and E. De Clercq[1]
Rega Institute for Medical Research[1] and Laboratory for Fytopathology and Plant Protection, Faculty of Agronomy[2], Katholieke Universiteit Leuven, Leuven, Belgium

The D-α-(1-3) and D-α-(1-6)mannose-specific lectins (agglutinins) from *Galanthus nivalis* (GNA), *Hippeastrum hybrid* (HHA), *Narciccus pseudonarcissus* (NPA) and *Listera ovata* (LOA) prevent infection of MT-4 cells by human immunodeficiency virus type 1 (HIV-1), type 2 (HIV-2) and simian immunodeficiency virus (SIV) at concentrations that are comparable to the effective concentration at which dextran sulfate molecular weight 5000 (DS-5000) inhibits these viruses (IC_{50}: 0.2-0.6 μg/ml). The mannose-specific lectins are much more effective than DS-5000 in inhibiting syncytium formation between persistently HIV-1- and HIV-2-infected HUT-78 cells (HUT-78/HIV) and uninfected Molt/4 (clone 8) cells. Both the plant lectins and DS-5000 interfere with the binding of anti-gp120 mAb (NEA 9284, Du Pont de Nemours, Brussels, Belgium) to gp120 expressing cells. However, in contrast with DS-5000, none of the plant lectins inhibit the adsorption of HIV-1 to the $CD4^+$ cells. These observations suggest that the D-α-(1-3)- and D-α-(1-6)-mannose-specific lectins achieve their anti-HIV activity through a mechanism that is different from that of the sulfated polysaccharides (dextran sulfate). While not inhibitory to virus adsorption, the D-mannose-specific lectins may be targeted at the subsequent step in the HIV replicative cycle, that is the fusion process.

66

Studies of the cellular pharmacology of the carbocyclic guanosine analog Carbovir, an inhibitor of human immunodeficiency virus.

A. Fridland,[1] L. Bondoc,[1] W.M. Shannon,[2] J.A. Secrist,[2] R. Vince.[3] [1]St. Jude Children's Research Hospital, Memphis, TN 38101; [2]Southern Research Institute, Birmingham, AL, 35255; [3]College of Pharmacy, University of Minnesota, Minneapolis, MN 55455 USA.

In light of the potent and selective antiviral activity of Carbovir (carbocyclic 2',3'-didehydro-2',3'-dideoxyguanosine) against the human immunodeficiency virus and as a part of our ongoing studies of the cellular pharmacology of purine dideoxynucleosides, we have investigated the mechanism for activation of this compound in human lymphoid cells. At an extracellular concentration of 10 μM, which blocks the cytopathic effect of HIV in vitro, carbovir was found to be metabolized to its mono-, di-, and triphosphates and to physiological guanine nucleotides. In situ conversion of carbovir to the triphosphate was slow and accumulated to a maximum concentration of about 0.02 μM. The metabolism of carbovir in mutants CEM cells deficient in both deoxycytidine kinase and adenosine kinase was found to be unchanged by comparison with parental cells. The studies also indicated that although carbovir enters the mitochondria it is not utilized by deoxyguanosine kinase and no significant accumulation of drug metabolites occurred in the mitochondria. While no phosphorylation could be detected with the known cellular kinases, a purified cytosolic 5'-nucleotidase catalyzed the initial phosphorylation of carbovir. Finally, we could demonstrate that a number of compounds could stimulate the accumulation of the putative active triphosphate of CBV. These observations may be of value in current attempts to develop effective combination chemotherapy for the control of AIDS. Supported by grants AI 27652, CA 43256 (CORE) P30 CA 21765 and American Lebanese Syrian Associated Charities.