90

Carboxy-terminal peptidomimetics of the herpes simplex virus ribonucleotide reductase small subunit inhibit viral replication and potentiate the antiviral activity of acyclovir. M. Liuzzi, R. Déziel, N. Moss, R. Plante, P. Beaulieu, R.L. Krogsrud, A.-M. Bonneau, J.G. Chafouleas and Y. Guindon. Bio-Méga/Boehringer Ingelheim Research inc., 2100 Cunard Street, Laval, Québec, H7S 2G5, Canada.

The ribonucleotide reductases (RR) encoded by the herpes simplex viruses (HSV) type 1 and 2 catalyze the conversion of ribonucleotides to deoxyribonucleotides that are required for viral DNA replication. Since the HSV RR is essential for optimal virus replication in cell culture and for virus-induced pathogenicity in several animal models, it has been proposed that the viral RR may constitute a potential target for antiviral therapy. The catalytically active HSV RR holoenzyme is formed by the reversible association of two homodimeric subunits of distinct molecular sizes. Subunit association can be selectively prevented by peptides that mimic the carboxy terminus of the enzyme's smaller subunit. These peptides bind to the enzyme's large subunit with concomittant loss of enzyme activity. In this report we will review our progress towards improving inhibitory potency against the RR and achieving antiviral activity against HSV in tissue culture assays. Furthermore, we will show that peptidic inhibitors (i) inhibit the production of deoxyribonucleotide triphosphate pools in HSV-infected cells, (ii) synergize with the antiviral nucleoside analogue acyclovir and (iii) inhibit replication of acyclovir-resistant strains of HSV. Taken together, our results demonstrate that inhibition of HSV replication is due to *in situ* inactivation of the viral RR. Thus, inhibition of the viral RR subunit association is a valid strategy to achieve inhibition of HSV replication.

91

Antiviral activity and mode of action of a sulfated galactan from Pterocladia capillaceae. E.B. Damonte*, C.A. Pujol*, M.I. Errea**, M.C. Matulewicz**, C.E. Coto*. *Laboratorio de Virología and **Departamento de Química Orgánica. Facultad de Ciencias Exactas y Naturales. Universidad de Buenos Aires. 1428 Buenos Aires. Argentina.

The antiviral effect of a sulfated galactan extracted with water at room temperature from the seaweed Pterocladia capillaceae was studied. This compound, named S1, proved to be a potent inhibitor of various herpesviruses without affecting cell viability. In plaque reduction assays in Vero cells, the mean ED50 values against HSV-1 and HSV-2 were 5.2 and 12.5 ug/ml, respectively, whereas concentrations greater than 200 ug/ml did not inhibit cell growth. To determine the point of inhibition of HSV-1 infection, Vero cells were treated with S1 at various times before and after HSV-1 infection. The compound was inhibitory of HSV-1 replication if it was added to the cells simultaneously with virus inoculum, but had no protective effect when it was not present in the adsorption medium. To ascertain the inhibitory mechanism of S1 on HSV-1 replication cycle, the kinetics of infectious virus adsorption to Vero cells was found to be highly altered in the presence of the compound. In addition, studies monitoring the attachment of radiolabeled HSV-1 virions to Vero cells in the presence and in the absence of the drug demonstrated that the mode of action of S1 could be attributable to an inhibitory effect on initial virus binding to the host cell.