115

Effects of Protease Inhibitors on the Cleavage of Influenza HA Glycoprotein Mimic by Human Respiratory Tract Protease

M.HOSOYA[1], S.MORI[2], H.SUZUKI[1],and S.SHIGETA[2]
Department of Pediatrics[1] and Microbiology[2], Fukushima Medical College, Fukushima 960-12, Japan

The hemagglutinin (HA) of influenza viruses undergo posttranslational proteolytic cleavage. The cleavage is accomplished by the host cellular protease. However, the protease which activate the HA glycoprotein in human respiratory tract is not characterized yet. Protease inhibitors such as camostat mesilate and nafamostat mesilate inhibit the replications of influenza virus A and B in vitro, in MDCK cell cultures, and in ovo, in chick embryos. We studied whether the protease inhibitors could inhibit the cleavage of synthetic substrate, which has a single arginine cleavage site, by crude pharyngeal secretion. The protease inhibitors inhibited the cleavage. The inhibitory concentration corresponded to the effective concentration at which the protease inhibitors inhibited the replication of influenza virus, in vitro and in ovo. These observation suggests that the protease inhibitors may inhibit the replication of influenza virus on human respiratory tract.

116

Inhibition of Influenza Viral Polymerases by Mini-RNA Genomes

Guangxiang Luo, S. Danetz, R. Colonno, and M. Krystal, Dept. of Virology, Bristal-Myers Squibb Pharmaceutical Research Institute, 5 Research Parkway, Wallingford, CT 06410, USA.

The 5'- and 3'-terminal sequences (13 and 12 nucleotides, respectively) of the influenza virus genome are highly conserved among all gene segments. In addition, the termini possess inverted complementary which allows for a partial duplex to form. This partial duplex RNA has been shown to play a major role in transcription, replication and assembly. Previous results from our group shown that *in vitro*, the viral polymerase complex (PB1, PB2, and PA) specifically binds to either the 5'-terminal nucleotides alone or to the 5'- and 3'-termini duplex RNA . The study presented here tests whether these partial genomes can act as competitive inhibitors of the viral polymerase *in vivo*. A system was designed to evaluate the antiviral activity of either 5'-, 3'- or both 5'- and 3'-termini containing RNAs inside mammalian cells. The results show that only the mini-genome RNA containing both the 5'- and 3'-termini sequences efficiently inhibited the activity of viral polymerase expressed from recombinant vaccinia viruses.

117

Inactivation Of Influenza And Other Viruses By *Pinorin*.

S.Kuznetsovs, M.Daugavietis, G.Ryazantseva Research Group BioLat, Riga, Latvia.

Pinorin (silbiol) was found to be the principal extractive constituents of Scots Pine needles coming from Latvia area of growth. The content, in terms of dry needle weight of silbiol is over 1%. The investigations *in vitro* and *in vivo* were carried out. *Pinorin* action was investigated in mice on experimental influenzal infection, caused by A-influenza virus Aichi/2/68 (H3N2). The obtained results suggest that *Pinorin* (silbiol) exerts an inactivating effect on different antigenic versions of A-influenza virus (H2N2, H3N2) and B and on Rhinovirus in immediate contact thus preventing the development of viral infection. In the concentrations above 100 mg/kg *Pinorin* exerts virucide action. In immediate contact with A-influenza virus its infection titer drop is 3,0 and over lg EID_{50}. *Pinorin* in the concentration of 100 mg/kg when intranazally administered half an our before and after 4 hours following contamination the inhibition of 13 type Rhinovirus reproduction in upper respiratory tracts in SwR strain mice is 1,5 lg $TCID_{50}$. *Pinorin* applycation during epidemic period in 1993-1995 reduced the risks of respiratory virus infections by 2-3 times.

118

SIGNIFICANCE OF DIFFERENT TESTS FOR PROGNOSIS OF ADVERSE REACTIONS OF ANTIINFLUENZA DRUGS

O.Kubar[1], N.Zacharova[2], H.Fucir[3],[1]Pasteur Institute, St.Petersburg, Russia; [2]Influenza Institute, St.Petersburg, Russia; [3]WHO Collaborationg Centre for International Drug Monitoring, Uppsala, Sweden.

It was done retrospective monitoring of adverse reactions of antiviral drug - Rimantadine in the time of its clinical trials and during practical use in patients.Both adverse reactions from central and peripheral nervous system disordes and psychiatric disorders are dominated in the structure of adverse reactions, which were registed in WHO Collaborating Centre for International Drug Monitoring from 1968 till 1995 years . The percentage of the adverse reactions from these systems was 45,5% among total number of reactions (148). On the base of data of neurologic examination of healthy volunteers which included: bioelectric brain activity, assesment of reactivity of autonomic nervous system (vascular reaction test, skin tempature, sweat secretion) and psychometric test; the score of testes for long - term prognosis of adverse reactions was obtained. These data may be used for correction of indication rimantadine and other amantadine compounds.