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AMANTADINE ANALOGUES BLOCK EARLY STEPS OF HIV INFECTION. A.G.Bukrinskaya, A.V.Serbin, O.P.Bogdan, L.L.Stotskaya, I.V.Alimova, Yu.N.Klimochkin. Central Institute of Doctors Advance Training, Russian Ministry of Health, A.V. Topchiev Institute of Petrochemical Synthesis, Russian Academy of Science, Moscow, Russia.

Newly developed polymeric adamantane analogues consisted of nontoxic water-soluble anionogenic poly-mer carrier and adamantane derivatives chemically linked to the carrier were tested for the inhibitory effect on HIV-I infection in lymphoblastoid cells, MT4. The effect of the drugs was registrated by ELISA p24 antigen capture assay and by immunoblotting with cell lysates. The concentrations of the compounds up to 400 μg/ml were not cytotoxic as determined by incorporation of ^{3}H-thymidine into acid-insoluble fraction. The drugs at the concentrations of 200 and 400 μg/ml fully inhibited HIV replication when the cells were pretreated 2h before infection. Profound antiviral effect was seen when the drugs were added just after virus adsorption and first 3 hours after adsorption. The compounds were not effective when added 4h after virus adsorption. Thus, the drugs affect early events of viral replication. The pretreatment of the cells with the polymeric carrier did not inhibit viral replication while adamantane component itself including the spacer group at the concentration presented in the compounds (32 μg/ml) produced antiviral effect closed to that of the compound. It follows that antiviral activity is provided by the adamantane component, and the polymeric carrier does not interfere with this activity. Amantadine and rimantadine hydrochloride at the concentrations higher than that in the compounds (100-200 μg/ml) were either inactive or only slightly inhibited viral replication.

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Inhibition of HIV-1 replication by Cyclosporin derivatives: mode of action studies.

R. Harrison, G. Werner, A. Billich, F. Hammerschmid, G. Palfi, P.Peichl and B. Rosenwirth; Sandoz Forschungsinstitut, A-1235 Vienna, Austria.

Activation of primary T4 cells was reported to be a necessary precondition for HIV replication. Immunosuppressive and non-immunosuppressive Cyclosporin derivatives were found to inhibit HIV-1 replication in various cell lines as well as in PHA-activated T4 lymphocytes. On the other hand, the immunosuppressant FK 506 was not active under these conditions, but was only inhibitory in T4 cells when give simultaneous with PHA. Thus, inhibition of cell activation cannot be the mechanism of the antiviral effect of Cyclosporin derivatives. Attempts were made to identify the step in HIV-1 replication being the target for this new class of anti-HIV compounds. Cyclosporin derivatives do not influence virus production by chronically infected cell lines but block de novo infection. Syncytia formation of chronically infected with uninfected T4 cell lines is not impaired by Cyclosporin derivatives. These results indicate a step between fusion and integration as the antiviral target. No inhibition could be detected in cell free assays of reverse transcriptase, protease and integrase using free compounds or Cyclophilin-bound Cyclosporin derivatives. Experiments are ongoing to analyze the effects of immunosuppressive and non-immunosuppressive Cyclosporin derivatives on the early events in viral nucleic acid synthesis.