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Phosphorylation of HIV-1 Matrix Protein is Necessary for Nuclear Targeting of Viral Preintegration Complex. A.G. Bukrinskaya[1], A. Ghorpade[2], A.M. Ragland[2], N.K. Heinzinger[2], T.E. Smithgall[3], R.E. Lewis[3], M. Stevenson[2], [1]D.I. Ivanovsky Institute of Virology, Moscow, Russia; [2]Department of Pathology and Microbiology, University of NE Medical Center, Omaha, NE; [3]Eppley Institute for Research in Cancer and Allied Diseases, University of NE Medical Center, Omaha, NE.

In the replication of HIV-1, gag matrix protein (MA) carries out opposing targeting functions. Myristoylation of gag MA allows membrane targeting of gag polyproteins, a modification required for virus assembly, while a nuclear localization signal at the N-terminus of gag MA facilitates the nuclear import of the viral preintegration complex during virus entry. Thus, a mechanism must exist which allows these opposing targeting functions to operate independently during virus assembly and infection. We now show that MA is phosphorylated during virus infection and phosphorylation is necessary to overcome MA membrane targeting properties. Inhibition of gag MA phosphorylation by inhibitors of tyrosine or serine kinase prevents MA-mediated nuclear targeting of viral preintegration complexes and impairs viral infectivity. The requirement for gag MA phosphorylation in virus infection is underscored by our finding that a cellular serine/threonine kinase is packaged within HIV-1 virions. These results reveal a novel level of regulation of HIV-1 infectivity and point to a novel target for antiviral agents which interrupt early events in HIV-1 infection.

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Phosphonate Derivatives of Six Membered-ring Nucleosides: Synthesis and Antiviral Evaluation. M.J. Pérez-Pérez[#], J. Balzarini[§], J. Rozenski[#], E. De Clercq[§] and P. Herdewijn[#]. [#]Medicinal Chemistry and [§]Experimental Chemotherapy, Rega Institute, B-3000 Leuven, Belgium.

Unsaturated derivatives of natural nucleosides (i.e. stavudine) and their carbocyclic analogues (i.e. carbovir) are well known antiviral agents. Despite the great number of modifications introduced into these compounds, there are only few reports on their ring enlarged six-membered analogues. Based on the antiherpetic activity shown by 1,5-anhydrohexitol nucleosides, whose sugar moiety is a six membered ring, we have undertaken the synthesis of nucleoside derivatives represented by the general formulae **I-III**, namely the "natural" series of nucleoside analogues (**I**), the carbocyclic analogues (**II**) and the isonucleosides (**III**). The phosphonomethoxy moiety was introduced as isosteric to the monophosphate function, in order to circumvent the first phosphorylation step. In this respect, it has been extensively described that phosphonate derivatives of acyclic and furanosyl nucleosides show potent antiviral activity, but there are almost no reports on the synthesis and antiviral evaluation of such derivatives with a six-membered ring sugar moiety. The 1,4-*cis* relationship between the heterocyclic base and the phosphonomethoxy moiety is derived from the structure of the above mentioned 1,5-anhydrohexitol nucleosides. The different strategies followed for the stereoselective synthesis of the three series of compounds, as well as the data from their antiviral evaluation, enzymatic recognition and chemical stability will be reported.