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Poster presentation

Macrocyclic polyamines inhibit HIV infection by interacting with the cellular HIV co-receptors CXCR4 and CCR5

Dominique Schols*[1], Sunil Hamal[2], Li Cui[2], Dana Huskens[1], Stefano Aquaro[3] and Thomas Bell[2]

Address: [1]Rega Institute for Medical Research, Department of Microbiology and Immunology, Katholieke Universiteit Leuven, B-3000 Leuven, Belgium, [2]Department of Chemistry, University of Nevada, Reno, NV, 89557-0216, USA and [3]Department of Experimental Medicine and Biochemical Sciences, University of Rome 'Tor Vergata', Rome, Italy

* Corresponding author

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Background

A number of macrocyclic polyamines and/or their metal complexes are known to have anti-HIV activity. For example, CADA compounds are triazacyclododecanes that specifically down-modulate CD4, the principal cellular receptor for HIV. Bicyclams and their metal complexes act as entry inhibitors by a different mechanism, via specific binding to the cellular co-receptor CXCR4. Manganese(II) complexes of certain penta-azacyclo-pentadecanes are superoxide dismutase mimics and reduce oxidative stress in cells; one such compound, M40401, has been reported to decrease apoptosis in HIV-infected astrocytes.

Materials and methods

By synthesizing and screening various pyridine-fused macrocyclic polyamines, we have discovered several lead compounds that act as HIV entry inhibitors by binding to one or both cellular HIV co-receptors, CXCR4 and CCR5.

Results

One of these new leads is SH06, the manganese(II) complex of a novel ring-fused pentaazacyclopentadecane. SH06 inhibits replication of HIV-1 IIIB and NL4.3 in MT-4 cell cultures with IC_{50} values of 0.2-0.4 μg/mL and with CC_{50} (cytotoxicity) of 20 μg/ml. Remarkably, SH06 interacts with both HIV co-receptors CXCR4 and CCR5, according to specific chemokine-induced calcium-signaling assays. SH06 acts as an antagonist toward SDF-1-induced Ca^{2+}-signaling in CXCR4-transfected cells (IC_{50}: 0.3 μg/ml) and inhibits SDF-1-induced chemotaxis of $CD4^{+}$T cells (IC_{50}: 0.5 μg/ml). However, SH06 acts as an agonist toward CCR5. In addition, the compound also has significant activity (IC_{50}: 0.8-4.9 μg/ml) against several X4 and R5 viruses in PBMCs and monocytes/macrophages.

Conclusion

New macrocyclic polyamines and their manganese complexes have been shown to interact with the HIV co-receptors CXCR4 and CCR5 and to inhibit HIV replication in various cell types. In particular, the manganese complex SH06 showed promising activity against X4 HIV-1, but also against R5 HIV-1. Analogs of this compound are of interest as potential novel chemokine receptor inhibitors and anti-HIV agents.