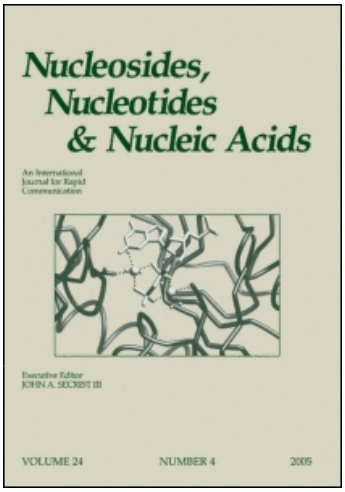

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Role of Adenosine Kinase in the Biological (Antiviral and Anticellular) Activities of Adenosine Analogues

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ROLE OF ADENOSINE KINASE IN THE BIOLOGICAL (ANTIVIRAL AND ANTICELLULAR) ACTIVITIES OF ADENOSINE ANALOGUES

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Abstract. A paired adenosine kinase-positive/adenosine kinase-negative cell system is proposed to distinguish those adenosine analogues that need to be phosphorylated to exert their biological effects from those that are mainly targeted at S-adenosyl-L-homocysteine hydrolase.

To assess the role of adenosine kinase in the biological properties of adenosine analogues, the latter were evaluated for their antiviral and anticellular activity in a paired cell system existing of adenosine kinase-positive (AK^+) wild type B-mix K-44/6 (Rous sarcoma virus-transformed) rat cells and an adenosine kinase-negative (AK^-) mutant cell line (clone D-4) derived thereof; both cell lines being devoid of adenosine deaminase activity[1].

Materials and Methods

Inhibition of virus-induced cytopathogenicity in vitro. The procedure for measuring inhibition of virus-induced cytopathogenicity has been described previously[2]. The antiviral activity was expressed as MIC_{50} or minimum inhibitory concentration required to reduce viral cytopathogenicity by 50 %.

Cytotoxicity. Cytotoxicity measurements were based on two parameters: (i) alteration of normal cell morphology and (ii) inhibition of cell growth. To evaluate cell morphology, confluent cell cultures which had not been infected, but were treated with various concentrations of the test compounds were incubated in parallel with the virus-infected cell cultures and examined microscopically at the same time as viral cytopathogenicity was recorded for the virus-infected cell cultures. A disruption of the cell monolayer was considered as evidence for cytotoxicity. To measure inhibition of cell growth, the cells were seeded in microtest plates (at 6,000 cells/well) in Eagle's minimum essential medium containing 10 % horse serum, and

4 h later various concentrations of the test compounds were added. The cells were then allowed to proliferate during 72 h at 37° C in a humidified, CO_2-controlled atmosphere. The growth of the cells was linear during this period. At the end of the incubation period, cells were trypsinized and enumerated in a Coulter counter. Cell growth-inhibiting activity was expressed as ID_{50}, that is the dose required to reduce the number of living cells by 50 %.

Results

According to their ID_{50} for cell growth and MIC_{50} for virus replication, the adenosine analogues could be clearly divided in two classes: I, those compounds that inhibited the growth of AK^+ cells at a 150- to 1500-fold lower ID_{50} than the growth of AK^- cells; these compounds also inhibited virus replication in AK^+ cells at a 1000- to 10,000-fold lower MIC_{50} than virus replication in AK^- cells; and, II, those compounds that were only slightly (5- to 15-fold) more inhibitory to AK^+ than AK^- cell growth and only 1- to 50-fold more antivirally active in AK^+ cells than in AK^- cells. To class I compounds belong tubercidin, toyocamycin, sangivamycin, β-xyloadenosine and α-lyxoadenosine, and to class II compounds belong 3-deazaadenosine (c^3Ado), carbocyclic 3-deazaadenosine (C-c^3Ado), (S)-9-(2,3-dihydroxypropyl)adenine [(S)-DHPA], (RS)-3-adenin-9-yl-2-hydroxypropanoic acid [(RS)-AHPA] (isobutyl ester) and neplanocin A.

Discussion

Apparently, the antiviral and anticellular activity of the class I compounds critically depends on phosphorylation by the host cell adenosine kinase, which means that these compounds are biologically active primarily as their phosphorylated products. Such phosphorylation seems to be of lesser or no importance for the class II compounds, which have all been recognized previously as potent inhibitors of S-adenosyl-L-homocysteine (SAH) hydrolase[3,4]. The present findings with the paired AK^-/AK^+ cell system are consistent with an action of the class II compounds targeted at SAH hydrolase.

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