Abstracts

Monday April 11

Oral Session I
Design of Antiviral Agents

Antiviral Activity of Acyclic Tubercidin Analogs. J.C. Drach, R.N. Nassiri, S.R. Turk, G.R. Birch, L.A. Coleman, C. Shipman, Jr., J.S. Pudlo and L.B. Townsend. Departments of Biologic and Materials Sciences and of Medicinal Chemistry, The University of Michigan, Ann Arbor, Michigan 48109, U.S.A.

A series of tubercidin analogs previously prepared in the laboratory of one of us (LBT) were evaluated *in vitro* for activity against HCMV and HSV-1 as well as for cytotoxicity. Tubercidin and 7-deazanebularin were active in antiviral assays but were equally cytotoxic. In contrast, slight antiviral specificity was found when 5-halogen-substituted tubercidin analogs were evaluated. These results led us to synthesize a series of acyclic 5-substituted tubercidin analogs. The parent compound of this series, 4-amino-7-(2-hydroxyethoxymethyl)pyrrolo[2,3-*d*]pyrimidine (acyclo-tubercidin), was inactive but 5-halogen-substituted compounds showed interesting activity. The 5-Cl, 5-Br, and 5-I analogs inhibited HCMV and HSV-1 at non-cytotoxic concentrations (I_{50} = 16, 3.9, 24 μM respectively for HCMV and 77, 11 and 250 μM for HSV-1). A similar order of potency was observed in yield reduction experiments (I_{90} = 46, 13, 14 μM respectively for HCMV and 50, 40 and >100 μM for HSV-1). In contrast no visual cytotoxicity was seen in HFF or BSC-1 cells at 100 μM. By DNA-DNA hybridization assay, the three analogs inhibited HCMV DNA synthesis by 50% at 4.3, 1.6 and 4.6 μM, respectively. Comparable inhibition of DNA synthesis in uninfected cells required concentrations of 11 to >100 μM; inhibition of RNA and protein synthesis required 94 to 350 μM. Analysis of inhibition of DNA synthesis by flow cytometry revealed the 5-Br-compound blocked DNA synthesis in S-phase. In conclusion, we consider the activity against HCMV to have therapeutic potential. This is somewhat surprising considering acyclovir is only slightly active against this virus. The work was sponsored by contract NO1-AI-42554 from N.I.A.I.D.