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Roles of Hydrophobicity, Protein Binding and the Probenecid-Sensitive Transport System in the Cerebrospinal Fluid Delivery of Nucleoside Analogues with Anti-Viral Activity.

Takeo Kawaguchi（川口健夫）, Masaki Kusumi（久住正樹）,
Tetsuya Hasegawa (長谷川哲也), Toshiyuki Nagata, Mineo Saneyoshi,
Masahiro Nakano[d] and Akinobu Hamada[d]

Faculty of Pharmaceutical Sciences, Josai University[a], 1-1 Keyakidai, Sakado, Saitama 350-0295 Japan, Tsukuba Research Laboratory, Toagosei Co.Ltd.[b], 2 Ohkubo, Tsukuba, Ibaraki 300-2611, J apan, Department of Biological Sciences, Teikyo University of Science and Technology[c], 2525 Yatsusawa, Uenohara, Yamanashi 409-0133, Japan, and Kumamoto University Hospital[d], 1-1-1 Honjo, Kumamoto 860-8588, Japan

Ten nucleoside analogues with anti-herpes or anti-HIV activity were investigated for their transport into the cerebrospinal fluid (CSF) following intravenous administration in rats. The novel anti-herpes agent 1-β-D-arabinofuranosyl-2-thio-5- fluorocytosine (5F-araSC) showed the highest CSF/plasma concentration ratio(>20%), while that of acyclovir (ACV) was very low (<5%). A linear relationship was observed between the partition coefficient (chloroform/water) and CSF /unbound plasma concentration in 6 of 9 agents. The exceptions were DDI, AZT and ACV, which showed much lower concentrations in the CSF than expected from their hydrophobicity and protein binding activities. The effects of probenecid treatment on the CSF and plasma concentrations were measured with continuous intravenous

administration of ACV, AZT, araC and 5F-araSC. Probenecid markedly increased the CSF concentrations of ACV and AZT, although the effect was m inimal in araC and 5F-araSC. These results may provide useful information for molecular design of nucleoside analogues with better transport to the brain.