188

The Transport of 9-(2-Phosphonylmethoxyethyl)adenine (PMEA) into Vero Cells
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The influx of 9-(2-phosphonylmethoxyethyl)adenine (PMEA) in uninfected and HSV-1 infected Vero cells was investigated using an initial velocity assay. Influx was found to require energy and to be sodium-dependent. The initial rate of PMEA influx was saturable with a K_m of 130 μM. All nucleoside mono-, di- and triphosphates (100 μM) tested exhibited >90% inhibition of the influx of 1 μM PMEA. The P_{2x} receptor agonist, β,γ-methyleneATP, and the P_{2y} receptor agonist, 2-methylthio-ATP both completely inhibited PMEA influx. 9-(2-Phosphonylmethoxyethyl)guanine (PMEG), 1-(2-phosphonylmethoxyethyl)cytosine (PMEC), (s)-9-(3-hydroxy-2-phosphonylmethoxypropyl) guanine (HPMPG), (s)-9-(3-hydroxy-2-phosphonylmethoxypropyl)adenine (HPMPA), and (s)-1-(3-hydroxy-2-phosphonylmethoxypropyl)cytosine (HPMPC) at 100 μM inhibited the influx of 1 μM PMEA by >50%. In contrast, most nucleosides, nucleobases, and inhibitors of nucleoside transport were ineffective in inhibiting PMEA transport, with the exception of adenosine (500 μM) and deoxyadenosine (500 μM) which inhibited the influx of 1 μM PMEA by 84% and 46%, respectively. Little or no inhibition was achieved with substrates or inhibitors of transport systems involving inorganic phosphate. In Vero cells infected with HSV-1 at an m.o.i. of 1, the initial rate of influx of 1 μM PMEA did not vary with time after infection up to five hours and was the same as the rate in uninfected cells. However, when the m.o.i. was increased to 10, the initial rate of PMEA influx was reduced to one-half that of uninfected cells throughout the 5-hr post-infection period. These results suggest that antiviral acyclic nucleoside phosphonates, such as PMEA, may enter cells via a carrier functionally distinct from those mediating nucleoside and nucleobase transport.

189

Transport of the Anti-Varicella Zoster Agent, 6-Methoxypurine Arabinoside and its 2'-O-Valerate Prodrug into Human Erythrocytes.
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The transport of the anti-varicella-zoster agent, 6-methoxypurine arabinoside (ara-M) and its 2'-O-valerate prodrug, 170U88, into human erythrocytes was investigated. The influx of ara-M was found to occur primarily by means of the nucleoside transporter: 1) Influx was nonconcentrative and saturable (K_m = 106 μM). 2) Inhibitors of nucleoside transport, nitrobenzylthioinosine, dipyridamole, and dilazep, inhibited the influx of 10 μM ara-M by >94%. 3) Influx was inhibited by nucleosides but not by nucleobases. 4) ara-M was a competitive inhibitor (K_i = 129 μM) of adenosine influx, and adenosine (K_m = 160 μM) was found to be a competitive inhibitor (K_i = 134 μM) of ara-M influx. By contrast, the influx of 170U88 occurred by means of nonfacilitated diffusion: 1) Influx was linearly dependent on 170U88 concentration. 2) Influx was not inhibited by nucleobases, nucleosides or inhibitors of nucleoside transport.