The Relationship between Passive Diffusion and Active Transport by P-Glycoprotein

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P-glycoprotein, P-gp, and related transmembrane efflux transporters bind a wide variety of toxins and drugs that insert into the cell membrane and export them at the expense of ATP hydrolysis. An overexpression of efflux transporters results in multidrug resistance, MDR, and, in turn, in failure of chemotherapy of e.g. cancers, epilepsy, bacterial, parasitic, and fungal diseases. To efficiently target drugs to cells protected by P-gp it is essential to know which drugs are able to reach the cytosol despite the presence of transporters. To this purpose we determined active efflux and passive influx for 15 drugs which are substrates for P-glycoprotein. The rate of P-gp-ATPase activation, V, which correlates with active efflux, was measured in MDR1 transfected cells by means of a Cytosensor Microphysiometer® which monitors the extracellular acidification rate in micro-pH units [1]. Passive influx, Φ, was estimated using two parameters derived from surface activity measurements, i.e. the air-water-partition coefficients, K_{aw}, and the cross-sectional area, A_D, of a drug [2]. For substrates with a small cross-sectional areas, A_D, ($A_D \sim 50$ Å^2) the rate of ATP hydrolysis (active efflux) is high, but passive influx, Φ, is even higher by up to three orders of magnitude. With increasing cross-sectional area, A_D, active efflux and passive influx decrease. However, passive influx shows higher size dependence than active efflux. *Net* transport, J, which is the difference between passive influx, Φ, and active efflux, V ($J = \Phi - V$) is therefore mainly observed for molecules with large cross-sectional areas whereas small molecules can reach the cytosol despite being substrates for P-gp [3]. For common P-gp substrates [4] the limiting area was found to be A_D 80 Å^2 [2]. This value is in close agreement with that obtained previously by means of a calibration diagram made with molecules of known ability to cross-the blood-brain barrier by passive diffusion [5, 6].

References:

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