Correlation between the kinetics of anthracycline uptake and the resistance factor in cancer cells expressing the multidrug resistance protein or the P-glycoprotein.

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Streszczenie

Multidrug resistance (MDR) in model systems is known to be conferred by two different integral proteins, the 170-kDa P-glycoprotein (Pgp) and the 190-kDa multidrug resistance-associated protein (MRP_1). One possible pharmacological approach to overcome drug resistance is the use of specific inhibitors, which enhance the cytotoxicity of known antineoplastic agents. However, while many compounds have been proven to be very efficient in inhibiting Pgp activity only some of them are able to inhibit MRP_1. The other likely approach is based on the design and synthesis of new non-cross-resistant drugs with physicochemical properties favoring the uptake of the drug by the resistant cells. The intracellular drug retention influences its cytotoxic effect. The level of the intracellular drug content is a function of the amount of drug transported inside the cell (influx) and the amount of drug expelled from the cell (efflux). In this work, the kinetics of drug uptake and the kinetics of active efflux of several anthracycline derivatives in both Pgp expressing K562/Adr cells and MRP_1 expressing GLC4/Adr cells was determined. Our data have shown that in both cell lines there is no correlation between the resistance factor and the kinetics of drug efflux by these pumping systems. However, a very good correlation between the resistance factor and the kinetics of drug uptake has been established in both cell lines: the resistance factor decreases when the kinetics of drug uptake increases. This work has clearly shown that when the rate of transmembrane transport of anthracycline is high enough, the efflux mediated by the protein transporter is not able to pace with it. The protein transporter essentially operates in a futile cycle and the resistance factor is tending to one. It does not mean, however, that when the resistance factor is close to one the anthracycline is not transported by the pump.