Effects of cholesterol on dye leakage induced by multidrug-resistance modulators from anionic liposomes

Madeleine Castaing[a], Alain Loiseau[b] and Leila Djoudi[a]

[a] GERCTOP-UMR6009, Faculté de Pharmacie, 27 Boulevard Jean Moulin, 13385, Marseille Cedex 05, France
[b] INSERM-IFR2, Faculté de Médecine Xavier-Bichat, Paris, France

„...characterised by specific changes in the intracellular cholesterol **metabolism** (Dessi et al., 1992). When treated with chemotherapeutic...Hydrophobicity of the drugs The Pallas 2.0 software program of **Compudrug** Chemistry Ltd. (Budapest, Hungary) was used to calculate the..."

Abstract

Multidrug-resistance (MDR) in cancer cells is often associated with marked changes in the membrane cholesterol levels. To assess the cholesterol-dependence of MDR modulator efficiency in terms of the drug-membrane interactions, the ability of 5 MDR-modulators to induce the leakage of Sulphan blue through anionic liposomes was quantified at various mole fractions x_{chol} of cholesterol (0–0.42). Depending on the electric charge of the drug, cholesterol modified to a large extent either the permeation dose inducing 50% dye leakage (PD_{50}) or the co-operativity (h) of the permeation process. The PD_{50} of Triton X-100 (non-ionic) and that of diltiazem and verapamil (mono-basic amines) varied only slightly (0.3 mM) with the cholesterol level, whereas the co-operativity increased by 1.9–2.7. On the reverse, the PD_{50} of a thioacridine derivative and mepacrine (di-basic amines) increased by 4.8–7.5 mM in the cholesterol range investigated, whereas the co-operativity (h) increased slightly (0.2–0.7). In the permeation process, the rate-limiting character of the electric charge (z) of the drug is likely to be strengthened by high cholesterol levels. The results provide evidence that in resistant tumours exhibiting high cholesterol levels, the MDR might be reversed by favourable drug-membrane interactions if the modulators are designed in the form of highly lipophilic mono-basic drugs that counteract the effects of cholesterol on the membrane dipolar potential and membrane fluidity.
Author Keywords: MDR-modulators; Cholesterol; Membrane permeation; Drug–membrane interactions; Multidrug-resistance; Cancer

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