Study of the drug-anionic lipid interactions in model membranes.

E. Goormaghtigh, P. Chatelain, J. Caspers and J.M. Ruysschaert.

Laboratoire de Chimie Physique des Macromolécules aux Interfaces, Université Libre de Bruxelles, C.P. 206/2, Boulevard du Triomphe, 1050 Bruxelles, Belgium.

A method allowing the study of the interactions between positively charged drugs and negatively charged membrane lipids is described. The method used permitted to demonstrate in model membrane the interaction between anthracycline drugs (adriamycin derivatives) and cardiolipin, a lipid specific of the inner mitochondrial membranes. This interaction would explain specific alterations observed on mitochondria (1, 2).
In the present work, dipalmitoylphosphatidylcholine and cardiolipine were spread at the air-water interface and adriamycin derivatives were injected into the subphase. We developed a new method using surface potential measurements to determine the association constant. 1) In a first step, the drug is injected into the aqueous subphase and the surface potential is recorded at equilibrium. The increase of the surface potential is function of both the monolayer charge density and the monolayer dipole reorientation after complexation.

2) In a second step, the ionic strength is modified by injecting a $NaNO_3$ saturated solution in the subphase. The surface potential change depends only on the remaining surface charge density. By comparison of this result with the Gouy-Chapman theory, an association constant can be calculated (table 1).

	K (1/M)	log P
Adriamycin	$1.8\ 10^6$	- 0.7
Cinerubin	$1.2\ 10^5$	- 0.2
Rubidazone	$3.1\ 10^5$	- 0.1
Nogalamycin	$2.7\ 10^5$	1.8
Rhodomycin	$1.5\ 10^5$	1.7
Steffimycin	No charge complexation	1.4

Table 1

As suggested by comparison of the octanol/water partition coefficient (P) and K for each drug, there is no direct relation between drug lipophilicity and drug-lipid interaction.

1. Duarte-Karim M., Ruysschaert J.M. and Hildebrand J. (1976) Biophys. Res. Commun. 71, 658-663.
2. Goormaghtigh, E., Chatelain P., Caspers J. and Ruysschaert J.M. (1980) Biochim. Biophys. Acta 597, 1-14.