

INTERACTION OF MAJOR PHOSPHOLIPIDS OF ERYTHROCYTE MEMBRANE'S INNER LEAFLET (PS, PE) WITH PHENOTHIAZINE METHANESULFONYLAMIDES

OLGA WESOŁOWSKA¹, ANDRZEJ B. HENDRICH¹, NOBORU MOTOHASHI² and KRYSTYNA MICHALAK¹

¹ Department of Biophysics, Wrocław University of Medicine, Chalubinskiego 10, 50-368 Wrocław, Poland, ² Meiji Pharmaceutical University, Noshio, Kiyose, Tokyo, Japan

Phenothiazine derivatives, such as chlorpromazine (CPZ) and trifluoperazine (TFP), cause erythrocytes' haemolysis when used in high concentrations. However in the concentration range of 20–30 μM they protect erythrocytes against hypotonic haemolysis and also cause stomato- and endocytosis [1]. Such shape changes are believed to be the result of preferential intercalation of cationic phenothiazine derivatives into inner leaflet of erythrocyte membrane [2] and their interaction with aminophospholipids: phosphatidylethanolamine (PE) and especially with negatively charged phosphatidylserine (PS). CPZ is also reported to cause partial and temporal scrambling of erythrocyte membrane components [3]. In this study we aimed to examine the interactions of aminophospholipids with newly synthesised derivatives: phenothiazine methanesulfonylamides having different substituents in tricyclic ring ($-\text{CF}_3$, $-\text{Cl}$, and $-\text{H}$). These compounds interact strongly with model PS membranes, as concluded from quenching of the fluorescence of NPN probe and shifting of its fluorescence maximum to longer wavelengths. Phenothiazine methanesulfonylamides also reduce the fluidity of PS membranes as shown by an increase of DPH polarisation degree. The interactions of phenothiazine derivatives with synthetic PE (DMPE) were studied by means of microcalorimetry (DSC). The thermal phase behaviour of DMPE is altered, and the appearance of two separated gel phases is observed. No changes in transition enthalpy caused by phenothiazines are detected.

REFERENCES

1. Isomaa, B., Hägerstrand, H., Paatero, G. Shape transformations induced by amphiphiles in erythrocytes. **Biochim. Biophys. Acta** 899 (1987) 93-103.
2. Sheetz, M.P. and Singer, S. J. Biological membranes as bilayer couples. A molecular mechanism of drug-erythrocyte interactions. **Proc. Natl. Sci. USA** 71 (1974) 4457-4461.
3. Schrier, S.L., Zachowski, A. and Devaux, P.F. Mechanisms of amphipath-induced stomatocytosis in human erythrocytes. **Blood** 79 (1992) 782-786.