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THE SURFACE AND MEMBRANE ACTIVITY OF TRIFLUOPERAZINE DIHYDROCHLORIDE

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The surface activity of phenothiazines (Florence, 1968) confers on this group of drugs the ability to interact with biomembranes. Trifluoperazine diHCl (TFP, donated by SKF) is one of the most active phenothiazines and in this study we have examined its effect on membrane systems above and below its apparent critical micelle concentration (CMC).

All drug solutions and phospholipid dispersions were prepared in pH 7.2 0.05M tris-HCl buffer, ionic strength .044. Surface tension measurements on TFP solutions by the method of Wilhelmy, using an anodised aluminium plate to allow wetting by the cationic drug solution, yielded γ vs. log C plots exhibiting a break around 0.4g l^{-1}(8.33×10^{-4}M) indicative of micellar aggregation. This CMC value was supported by the results of conductance measurements at 22° in a Pt cell, cell constant 1.34cm^{-1}, (Wayne-Kerr Universal Bridge B224). The CMC here is low compared to the value obtained by Attwood and Natarjan (1981) which may reflect the CMC-pH-dependence of TFP which has two ionisation centres on the piperazine moiety. Obvious interfacial activity was exhibited by TFP at concentrations well below the CMC in model membrane systems. Surface pressures (Lauda balance) of dimyristoyl lecithin (DMPC) monolayers spread on TFP solution subphase show that TFP penetration of the monolayer occurs at high areas/DMPC molecule at subphase concentrations as low as 10^{-5}M TFP. As the monolayer is compressed however, TFP is ejected so that the area per DMPC molecule of the condensed monolayer on TFP buffer solution subphase is essentially the same as on buffer subphase. Similarly differential thermal analysis (DTA) of hand shaken DMPC 5% w/v dispersions shows that at concentrations as low as 5×10^{-9}M, TPF added to the external aqueous phase appeared to penetrate the phospholipid bilayers and decreased the enthalpy changes (ΔH_t) associated with the gel-liquid transition observed at 23° (T_c). The area under the endothermic peak decreased with increasing TFP concentration, although no significant change in T_c was detected.

Above the CMC of TFP the DMPC transition endotherm was completely abolished as long as the DMPC concentration was less than its maximum additive concentration for the system. This loss of the transition endotherm presumably indicates solubilisation and thus loss of the ordered phospholipid bilayer structure. DMPC monolayers were also at least partially solubilised at supra-CMC TFP subphase concentrations shown by low surface pressures for small areas per DMPC molecule. Microscopic observation of cultured cells exposed to similar concentrations of TFP reveals gross damage to the cell membrane with cell rupture and cytoplasmic release.

Micelle formation then is not a prerequisite for the membrane activity of TFP but above the CMC its action on membrane models changes qualitatively and promotes gross disorder in phospholipid structures.

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Attwood, D. and Natarjan, R. (1981) J. Pharm. Pharmacol. 33: 136-140.

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