INTERACTION OF ORGANOTIN COMPOUNDS WITH PHOSPHOLIPID MEMBRANES

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Organotin compounds are used as stabilizers in the production of plastics, agricultural pesticides and preservatives of paper and textiles. They are important contaminants in the environment which have deleterious impact on aquatic ecosystems and are potential toxicants in humans and other species.

The extensively used organotin compounds, tributyltin (TBT) and triphenyltin (TPT) have broad biological activities. They function as ionophores [1] and their mechanism of toxicity appears to be strongly dependent on organotin lipophilicity [2]. TBT and TPT are membrane-active molecules, their mode of action involves the membrane as their site of action, and includes haemolysis [2], release of calcium from sarcoplasmic reticulum [3], inhibition of histamine release [4], perturbation of membrane enzymes [5, 6] and induction of apoptosis in lymphocytes [7].

The interaction of organotin compounds and membranes plays a potential role in their toxic mechanism. It has been suggested that the effect of organotin compounds on liposomal membranes is dependent on the anion moiety and the phospholipid characteristics [8] and that their lipophilicity and polarity together with the surface potential and environment of the lipid molecules are important factors in the interaction with model membranes [9].

To further understand the influence of organotin compounds on the lipid component of membranes, we studied the effect of TBT and TPT on the thermotropic and structural properties of phosphatidylcholine and phosphatidylethanolamine, two essential phospholipids in eucaryotic membranes.

In the absence of organotin compounds, dimiristoylphosphatidylcholine (DMPC) exhibits two endotherms upon heating, a pretransition and the main gel to liquid-crystalline phase transition. The presence of low concentrations of organotin compounds abolishes the thermotropic pretransition. Increasing concentrations of TBT progressively broadens the main transition and causes a shift to lower temperatures. In the samples containing a high proportion of TBT, the presence of two endotherms is apparent. The influence of TPT is qualitatively similar to that of TBT although less pronounced, so that the main transition is not so broad and the presence of the second endotherm is less

apparent. Organotin compounds heighten the enthalpy change of the transition and shift T_m to lower temperatures, although both effects are smaller in the case of TPT.

In the case of dimyristoylphosphatidylethanolamine (DMPE), the incorporation of TBT and TPT does not significantly change the thermogram of the transition. Both compounds induce an increase in the enthalpy change of the transition which is much smaller than in the case of DMPC, being the effect of TBT larger than that of TPT. The temperature of the transition is not affected by these compounds.

The observed effects of organotin compounds on DMPC are compatible with the hydrophobic butyl and phenyl moieties aligning themselves with the prevailing directions of the phospholipid acyl chain, where they can disrupt its packing, reduce the cooperativity of the transition and shift the phase transition temperature to lower values. The interaction of the phospholipid acyl chains with the hydrophobic moieties of TBT and TPT would enhance the hydrophobic interactions in the chains. As a result of this, the enthalpy change of the transition from the gel to liquid-crystalline phase is drastically increased in the presence of organotin compounds. The appearance of a second component in the thermogram when the concentration of organotin compounds is increased can be explained by the formation of TBT- or TPT-enriched domains similar to those described for other toxicants like abietic acid [10]. We have shown that organotin compounds interact with the interfacial region of dipalmitoyl-phosphatidylcholine and make the carbonyl groups less accessible to water [11], supporting the hypothesis that organotin compounds are located in the upper part of the phosphatidylcholine palisade.

The effect of organotin compounds on phosphatidylethanolamine system is different. They do not affect the transition temperature of DMPE and influence the enthalpy change of its transition to a lesser extent than that of DMPC. It is known that the small head group of phosphatidylethanolamines together with the formation of intermolecular hydrogen bonding allows a very close packing of these phospholipids. It seems that the highly packed DMPE molecules are not miscible with organotin compounds and they are segregated in the membrane. Hence, these compounds only slightly affect the thermotropic transition of the phospholipid.

In summary, it has been shown that organotin compounds are incorporated in phosphatidylcholine and phosphatidylethanolamine, i.e. the most abundant phospholipids in eucaryotic membranes, and that their interaction depend on the type of lipid. While organotin compounds seem to be excluded from the phosphatidylethanolamine systems they greatly perturb the physical structure of phosphatidylcholine systems. The perturbation of the membrane structure exerted by organotin compounds could affect membrane function and may mediate some of their toxic effects.

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