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A Model for the Transfer of Conformational Change in the Phospholipid Headgroup towards the Hydrophobic Interior of the Membrane *via* a P^V Trigonal Bipyramidal Intermediate

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Abstract: Co-ordination change of phosphorus may be responsible for a decrease of the cross-sectional area of the phospholipid headgroup and a reduction of the difference in effective chain length between both acyl chains of a phospholipid molecule. Both factors induce a change in the angle of tilt of the acyl chains, leading to increasing or decreasing lateral phase separation.

Recently, the coexistence of liquid-crystalline and gel-like domains (clusters) is reported for mixtures of phosphatidylcholine (PC) with phosphatidylethanolamine (PE)¹, cholesterol² or proteins³. This occurs in the phase transition region, ranging from the main phase transition temperature down to a temperature around the pre-transition. It should be seen as a continuously varying degree of congregation of more ordered molecules in a liquid-crystalline matrix and *vice versa*, effectuating a gradual increasing or decreasing lateral phase separation. The resulting variation in molecular density is accompanied by a local variation in the angle of tilt of the lipid hydrocarbon chains relative to the bilayer-normal. The degree of lateral phase separation will depend on internal factors as miscibility⁴ and interaction energies between the constituents³ and can, besides by temperature, be influenced by a number of external factors e.g. water content⁵, proton and cation concentration⁶, ionic strength⁶ and potential field⁷. For the physiological process of the excitation of an axon⁸, we propose a model in which a change in the degree of phase separation originates in the headgroup of the phospholipids, at the level of an interconversion of P^{IV} into P^V trigonal bipyramidal intermediate (TBP). This P^V geometry effectuates a decrease in cross-sectional area of the phospholipid headgroup and diminishes the difference in chain length between the lipid hydrocarbon chains. As will be explained, both factors will change the angle of tilt of the hydrocarbon chains, which will lead to the lateral phase separation. During the excitation of an axon the decrease in cross-sectional area of the headgroup is visualized at a molecular level by the following changes. Ca^{2+} ions desorb from the outer monolayer of the membrane⁹ and the charge at the inside of the membrane inverts from negative to positive⁸. By these changes the headgroup is no longer forced in an extended and inward pulled conformation and gets the opportunity to reorientate, as can be seen in the figure.

The existing $P^{IV} \rightleftharpoons P^V$ equilibrium, under 'resting' conditions laying at the side of the P^{IV} compound, will be shifted in the direction of the P^V intermediate, because this conformation is stabilized by the formation of a diequatorial pseudo six-membered ring. The positively charged nitrogen of the choline headgroup shields the negative charge of the formerly double bonded oxygen, thus polarizing the P=O bond, by which the electrophilicity of the phosphorus atom will be increased¹⁰. This process will be promoted by the nucleophilic attack of a water molecule, normally present in excess in the headgroup layer of the membrane, thus generating a P^V TBP intermediate. In molecules as PC, where the headgroup in 'stretched' form will occupy a greater excluded cross-sectional area than the lipid hydrocarbon chains², the chains originally adopted a tilted conformation to fill in a potential void in the hydrocarbon chain region². The decrease in cross-sectional area of the headgroup due to ringformation, will cause decrease in the angle of tilt of the hydrocarbon chains. PE and N-methyl and N,N-dimethyl PE do not exhibit such pretransition behaviour due to the smaller excluded area of the headgroup in 'stretched' conformation¹¹. The reduction of the difference in chain length between the hydrocarbon chains, originates in the increased electron density accumulated on the apical ligands in a P^V TBP geometry¹⁰. The increase in electron density on the apical oxygen, through which the phosphate is bound to the glycerol backbone, brings about a repulsion of the sn-2 oxygen, as indicated in the figure. This repulsion is theoretically verified for the P^V TBP model compound derived from tetrahydrofurfurylphosphate, in which the same O-C-C-O-P sequence occurs at the apical position in a TBP intermediate¹². Rotation around the C₂-C₃ bond of the glycerol backbone shifts the sn-2 chain in the direction normal to the bilayer and reduces the difference in effective chain length between the hydrocarbon chains. Comparison of ¹³C and ²H NMR spectra of phospholipids, labelled respectively with ¹³C at the sn-2 carbonyl group and with ²H at the 4-position of the sn-2 chain, suggests that a conformational change of the carbonyl group precedes chain melting on increasing temperature¹. Moreover PCs with miristoyl, palmitoyl and stearoyl chains at the sn-1 and/or sn-2 position show strong dependence of the pretransition behaviour on composition¹³. Co-operative change in the angle of tilt of a number of phospholipid molecules is needed to maximize the van der Waals interactions between neighbouring acyl chains. This will lead at macromolecular level to the formation of a cluster with an angle of tilt differing from the surrounding matrix. The relaxation time of such a cluster is appreciable greater than that for other characteristic movements of the molecule¹⁴. The short-living P^V TBP intermediate initiates the formation of a cluster with a much longer life-time, through which a timescale can be reached at which physiological processes (like those occurring during a nerve impulse) can take place¹⁵.

It is tempting to correlate the Na⁺ channel opening during the excitation of an axon to a change in degree of lateral phase separation of the membrane-protein system. The hysteresis between the fast order-disorder transition and the relative slow disorder-order transition makes a lipid bilayer extremely suitable to follow oscillating processes and to store short-living information, as required to pass a nerve impulse¹⁵. Measurements of valinomycin-mediated potassium conductivity around the region of lateral phase separation in binary mixtures show a pronounced maximum in electrical conductivity at the main phase transition temperature¹⁶. One can imagine an integral protein in a fluid environment to be free to adopt the tertiary structure necessary to function as an ion channel. A gel-like matrix can displace some special group of the channel-forming protein out of its critical position¹⁷ and/or disturb an unbroken protein in helix form¹⁸. It might offer support for the above mentioned supposition that 2-amido-PC, contrary to PC, is found to be inhibitory for integral proteins¹⁹. The oxygen esterified to C₂ of the glycerol backbone is essential for the transfer of the conformational change in the headgroup towards the difference in chain length between the hydrocarbon chains. If this oxygen is replaced by the less electronegative nitrogen, less repulsion and resulting acyl chain shift will be expected. Moreover, the hydrogen bridge found in X-ray analyses of comparable lipids²⁰, will hinder acyl chain shift and headgroup reorientation.

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