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REFINEMENT OF THE FLUID-MOSAIC MODEL OF MEMBRANE STRUCTURE

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Summary

Certain molecular packing criteria previously employed in a quantitative analysis of lipid micelles and bilayers are here extended to biological membranes. The inclusion of both thermodynamic and packing considerations point to a highly complex self-assembly mechanism in which the organization of lipids and proteins is highly coupled, with far reaching consequences as regards the structure and function of biological membranes.

Certain geometric packing criteria previously employed in a quantitative analysis of the structural properties of lipid micelles, bilayers and vesicles [1,2] are here extended to membranes composed of both lipids and proteins. A picture emerges in which the organization of lipids and proteins in membranes is highly coupled, with important consequences as regards the structure of biological membranes. The proposed model is a refinement of the Fluid-Mosaic model [3] in that both thermodynamic and molecular packing factors are considered together.

As in the Fluid-Mosaic model, we shall assume that there are no strong specific intermolecular interactions which rigidly bind different lipids and proteins. In this case the hydrophilic surface (head-group) area per lipid may be taken as effectively constant for any particular lipid. We also assume that lipid hydrocarbon chain region is in a fluid-like state, so that it can take up any shape so long as it does not extend farther from the head-group than a certain "critical length" (roughly equal to, but somewhat less than, the fully extended molecular length of the hydrocarbon chains [1,4]). As regards the proteins, initially they will be assumed to be rigid and globular, with surfaces

characterized by distinct hydrophilic and hydrophobic areas [3].

Fig. 1a (left) shows a schematic drawing of a rigid globular protein embedded in a planar lipid bilayer [3]. Such an arrangement is energetically not allowed since it contains a void or vacuum region, which cannot be filled without the bilayer becoming distorted from its planar shape (see legend to Fig. 1). Fig. 1a (right) shows the same protein surrounded by lipids whose arrangments are consistent with both packing and thermodynamic restrictions. In order to fill the void region the lipid hydrocarbon chains have deformed whilst keeping the hydrocarbon volume and lipid surface area unchanged, and at the same time not extending beyond their "critical length".

At this point we may already note a number of important corollaries. First, proteins may not in general be thought of as floating freely in an indifferent sea of lipid, even when the lipids are in a liquid-like state, since packing constraints impose a structural coupling between proteins and their neighbouring lipids (this being a purely geometric effect, and is in addition to any specific interactions, such as Ca^{2+} binding, which may lead to more strongly coupled boundary lipids). Second, the lipids near the protein must have hydrocarbon chain configurations different from those in the rest of the bilayer. This difference leads to different mobilities of the chains near a protein and manifests itself in changes of such measurable properties as the

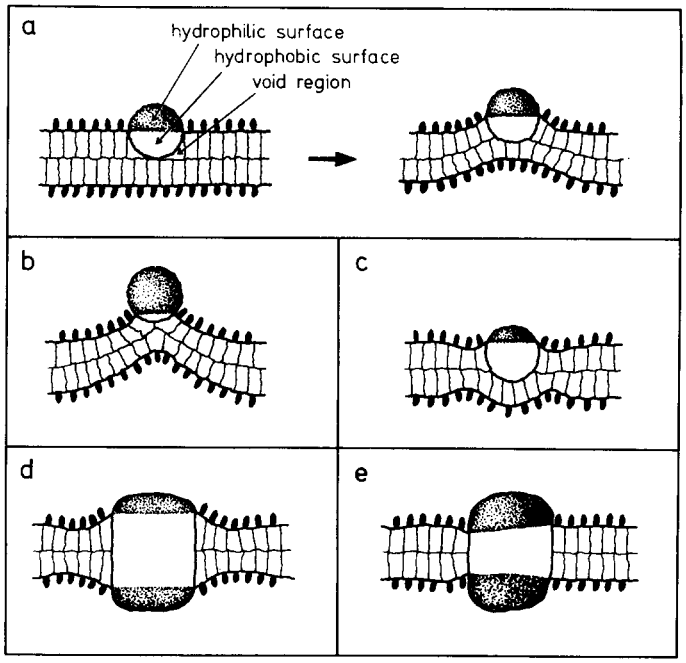

Fig. 1. a (left), drawing of spherical protein embedded in a planar bilayer. Such a structure is not allowed since it contains a void region. (For a spherical globular protein of radius r = 15 Å the void area would be about $5\pi r^2$. Since hydrocarbon surface energies are typically of order 25 erg/cm^2, this void area would have an unacceptably large energy, in excess of 200 kT). For this void region to be filled the lipids have to deform from their planar bilayer configuration. a (right), Arrangement of lipids around the protein consistent with packing requirements. b—e, diagrammatic illustrations of the way lipid bilayers structure around different globular proteins consistent with both packing and thermodynamic restrictions.

order parameters of hydrocarbon chains, as measured by ESR or NMR [5—7]. Third, packing constraints affect the lipids in the upper and lower halves of the bilayer in different ways. Fourth, the lateral motion of proteins (and lipids) in membranes would be affected by the presence of a structurally coupled region.

Figs. 1b—1e illustrate how proteins of different shapes and hydrophobic-hydrophilic areas modify a lipid bilayer in their vicinity. In those examples the proteins have been so chosen (drawn) that the lipids can be accommodated around them without being unfavourably packed. Clearly, many proteins and lipids would not be able to be so accommodating to each other. Indeed, in Fig. 1c the lipids surrounding the protein in the lower half of the bilayer may not be able to sustain the large convex curvature needed to envelop the lower hydrophobic region of the protein without an increased surface head-group area which is energetically unfavourable [1]. In a real biological membrane consisting of a variety of lipids each having different packing properties [1,2] those lipids that can pack favourably into such a region of high curvature would be preferentially drawn into this region. The fifth corollary, therefore, is that for a multicomponent lipid-protein membrane there may be an effective phase separation of boundary lipids around a protein (similar to the demixing of phosphatidylethanolamine and cholesterol in phosphatidylcholine-phosphatidylethanolamine-cholesterol bilayers [8] arising from the incompatible packing of phosphatidylethanolamine and cholesterol [2].

The different hydrocarbon chain configuration of lipids near a protein must have associated with it a different configurational entropy from that in the rest of the bilayer. For example, in Fig. 1d the hydrocarbon chains near the protein are forced to extend farther than those in the rest of the bilayer. For example, in Fig. 1d the hydrocarbon chains near the protein are forced to extend farther than those in the rest of the bilayer. These chains would therefore be motionally restricted and consequently have a lower configurational entropy (in effect, packing constraints have forced these chains to become less liquid-like). Such an effect leads to an attractive interaction between two such proteins [9], since by coming together the boundary lipids are ejected into the free bilayer where their configurational entropy is higher. If this attractive interaction is sufficiently strong it would result in adhesion of proteins as shown in Figs. 2a and 2b. On the other hand, the proteins shown in Fig. 2a would repel those in Fig. 2b (this interaction is analogous to that between two floating bodies in water, which depends on the shapes of the menisci at the surfaces of the bodies).

Fig. 2c shows how two different proteins on opposite sides of a membrane may associate favourably with each other, since by coming together the configurational entropy of the lipids is again increased.

In order for the present model to be put on a quantitative footing we must have more detailed knowledge of the tertiary conformations of proteins. In all the illustrations I have complied with the convention [3] of drawing the proteins as rigid globular structures, possessing large distinct surface areas that are either hydrophobic or hydrophilic. Accepting that this

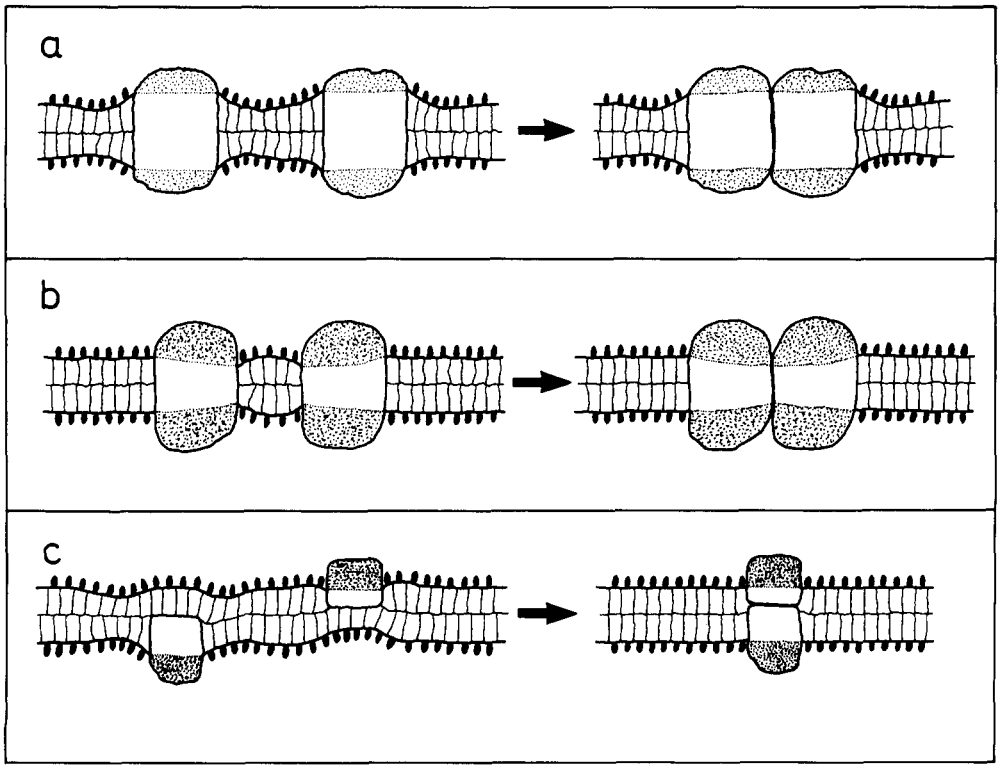

Fig. 2. Packing constraints affect the hydrocarbon chain configurations and mobilities of lipids near proteins. If the configurational entropy of these boundary lipids is lower than that of lipids in the rest of the bilayer the proteins attract each other [9].

is often the case one is confronted with at least two explanations for this: either these proteins have been selected for their job by an evolutionary process, or each protein can take on a number of different but rigid conformations depending on its environment and, when this is a bilayer, it takes on that conformation which allows it to be most favourably incorporated into the bilayer (with minimal deformation of the bilayer). Kimelberg and Papahadjopoulos [10], in a discussion of the possible mechanisms by which proteins increase the permeability of phospholipid membranes, earlier suggested that both protein conformation and the packing of the acyl chains may be perturbed as proteins penetrate phospholipid bilayers and monolayers. For certain proteins, therefore, we may expect their conformation and hence their function to vary with the types of lipids (and other proteins) in their vicinity. Such conformational changes may also be induced by changes in ionic strength (e.g. Ca ion concentration) and pH, which affect the packing properties of ionic lipids. Thus in general, both lipids and proteins may deform, as well as cluster, in order to accommodate each other favourably in a membrane.

The main point of this report is to emphasize and illustrate that thermodynamic as well as packing effects must be considered together in any

attempt at understanding the organization and function of biological membranes at the molecular level.

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