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Review

Lipid modulation of ion channels through specific binding sites☆,☆☆

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ABSTRACT

Ion channel conformational changes within the lipid membrane are a key requirement to control ion passage. Thus, it seems reasonable to assume that lipid composition should modulate ion channel function. There is increasing evidence that this implicates not just an indirect consequence of the lipid influence on the physical properties of the membrane, but also specific binding of selected lipids to certain protein domains. The result is that channel function and its consequences on excitability, contractility, intracellular signaling or any other process mediated by such channel proteins, could be subjected to modulation by membrane lipids. From this it follows that development, age, diet or diseases that alter lipid composition should also have an influence on those cellular properties. The wealth of data on the non-annular lipid binding sites in potassium channel from *Streptomyces lividans* (KcsA) makes this protein a good model to study the modulation of ion channel structure and function by lipids. The fact that this protein is able to assemble into clusters through the same non-annular sites, resulting in large changes in channel activity, makes these sites even more interesting as a potential target to develop lead compounds able to disrupt such interactions and hopefully, to modulate ion channel function. This article is part of a Special Issue entitled: Membrane structure and function: Relevance in the cell's physiology, pathology and therapy.

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Abbreviations: BK, big potassium channel; BN-PAGE, blue native polyacrylamide gel electrophoresis; Ca_v, voltage-gated calcium; CNG, cyclic nucleotide-gated channels; CRAC, cholesterol binding sites; CTD, cytoplasmic domain; ENaC, epithelial sodium channels; FRET, Förster resonance energy transfer; $GABA_A$, γ-aminobutyric acid-gated channel; GIRK, G protein-coupled inwardly-rectifying potassium channel; HCN, hyperpolarization-activated cyclic nucleotide-gated channel; hERG, human Ether-à-go-go-Related Gene potassium channel; HOP, high opening probability pattern; IP_3R, IP_3-gated calcium release channels; K_{ATP}, potassium channel activated by intracellular ATP binding; KCNQ, potassium voltage-gated channel subfamily KQT; KcsA, potassium channel from *Streptomyces lividans*; Kir, inward-rectifier potassium channel; K_v, voltage-gated potassium channel; LOP, low opening probability pattern; MscL, large-conductance mechanosensitive channel; nAChR, nicotinic acetylcholine receptor; PA, phosphatidic acid; PC, phosphatidylcholine; PG, phosphatidylglycerol; PIP_2, phosphatidylinositol 4,5-bisphosphate; PUFAs, polyunsaturated fatty acids; RyR, ryanodine-sensitive calcium release channels; SUR, sulfonylurea receptor; TMD, transmembrane domain; TRP, transient receptor potential channels; TRPL, transient receptor potential-like *Drosophila* phototransduction channels; VDAC, voltage-dependent anion channel.

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1. Introduction

Ion channels play important physiological roles in all living organisms, from prokaryotes to higher animals. Cell excitability, muscle contraction, synaptic transmission and cell signaling are among the processes mediated by this large family of proteins [1,2]. This is the reason why they have become a central target for developing new drugs against pathologies related to those processes, referred as channelopathies [3].

Ion channels are integral membrane proteins surrounded by a complex milieu of lipid molecules that, far from being just a passive barrier, play an active role in their structural and functional modulation. These effects are especially relevant for those proteins undergoing conformational changes/movements at their membrane-embedded domains, as it is the case of ion channels. However, the mechanism through which lipids exert such modulation remains elusive. Basically two different but not mutually exclusive modes of interaction between lipids and membrane proteins have been suggested. On one hand, there are non-specific interactions through which general physical properties of the membrane would influence protein structure and function. These include the hydrophobic mismatch between lipids and proteins that elicit lipid and/or protein deformations in order to avoid the energetic cost of exposing hydrophobic areas to water; interfacial curvature that determines the capacity of the membrane to deform as to avoid the mentioned hydrophobic mismatch; as well as membrane surface tension, lipid free volume, viscosity and lateral pressure profile, which establish the resistance of the lipid ensemble to the conformational movements of the protein (for a review see [4–6]). Basically all these parameters influence the packing and/or the conformational movements of membrane proteins within the lipid membrane, especially those that involve a considerable change in the protein volume or lipid-exposed surface, as it is the case in the mechanosensitive ion channels [7,8]. On the other hand, there is increasing evidence for the modulation of the structure and function of ion channels through a direct interaction with certain lipids, which is the scope of this chapter. Two different classes of bound lipids for such direct interactions have been defined, the annular ones, which would correspond to the first layer of lipids surrounding the transmembrane portion of the membrane protein; and the non-annular ones, that would be bound to certain grooves especially between protein subunits.

2. Lipid modulation of ion channel activity

Although there is a large heterogeneity in the structure of ion channels, all of them share a common feature: their structure contains transmembrane domain (TMD) which can move within the membrane bilayer to adopt diverse conformations associated to different functional states. This fact makes ion channels ideal candidates to be modulated by its lipid ensemble. Several modes have been proposed to explain how lipids bound to ion channels could modify their function [5].

1) Charged lipids alter the concentration of charged species close to the membrane that could affect ion channel activity. For instance, anionic lipids increase the negative charge at the membrane surface and therefore enhance the concentration of positively charged molecules close to the membrane. For a cation channel this could lead to an increased current and selectivity for cations over anions. Moreover, the higher local concentration of protons, Ca^{2+}, etc. could also modulate the channel activity in an allosteric-like manner. In the case of protons, for example, they would neutralize acid residues close to the membrane, thus increasing the relative hydrophobicity at that region of the protein.
2) Lipid headgroups can stabilize the α-helical ends of membrane proteins, so also their helix packing. This depends on their capacity to form hydrogen bonds with the amino acids at the ends of such helixes.
3) The acyl chain length and intrinsic interfacial curvature of lipids bound to the protein can also be determinant for channel structure and function. If there is a large hydrophobic mismatch between the lipids and the protein, this could force the adoption of a non-functional protein structure, or else favor the conformation state where that mismatch is reduced. These changes include the tilting or alterations in the packing of protein domains.
4) Specific lipids are often bound to intersubunit protein grooves, enhancing the stability of the protein and probably facilitating their movements, acting as a “lubricant”.

There are several studies that have contributed to an increasingly refined model of this complex issue. The role of lipids on the function of voltage-gated channels seems particularly interesting. These proteins have voltage-sensor domains formed by the transmembrane helix S4 and part of the helix S3 (Fig. 1), which are thought to undergo a considerable movement through the membrane in response to a change in the membrane potential. Some authors suggest that negatively-charged phosphate groups in membrane lipids would help to stabilize specific positively-charged, voltage-sensing residues during the voltage-sensor gating process [9]. It is believed that lipid binding to such domains could explain their influence on the activation of these ion channels [10–12]. Alternatively, other authors propose that instead of specific lipid–protein interactions, annular lipids as a body would act as stabilizers of the voltage-sensor paddle in an active conformation. Thus, in this respect, the annular lipids and the protein would form a functional unit. Moreover, the lipid headgroup capacity to form hydrogen bonds has been pointed out as a key factor for the lipid to exert such effect. As a corollary, any molecule able to disturb the lipid annulus, such as cholesterol, would also be expected to affect the activation of these channels [13].

Other lipids such as certain polyunsaturated fatty acids (PUFAs) would exert their direct effect on ion channels through domains that do not involve the voltage sensor but undergo also rearrangements during the inactivation process. PUFAs inhibit most of the voltage-gated ion channels, although in some cases the opposite effect has also been reported [14]. In addition to the effects on the magnitude of the ionic currents, it has been shown that arachidonic acid (a 20-carbon omega-6 polyunsaturated fatty) converts the K_v delayed rectifiers into A-type rectifier channels. In general, PUFAs seem to act as open-channel blockers of K_v channels, eliciting an increase in the rate of inactivation. Thus, the observed process might be analogous to the N-type inactivation by the Kvβ1 auxiliary subunits. From studies on the time- and voltage-dependent interaction with K_v11.1 channels, it has been suggested that PUFAs preferentially bind to the open state of these channels [15]. Oliver and collaborators [16] explain these results, in the case of the arachidonic acid, by proposing that it inserts into the cell membrane from either side, interacts with the channel protein

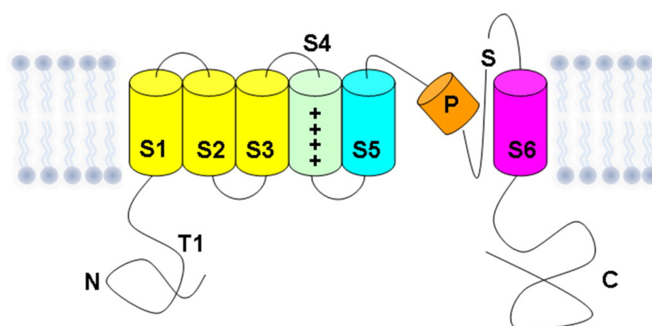

Fig. 1. Schematic representation of the membrane topology of K_V channels. S1 to S6 represent the six transmembrane segments, where S4 corresponds to the voltage sensor. S5 and S6 form the pore domain that includes the pore helix (P) and the signature sequence (S) N- and C-terminal domains are indicated as N and C, respectively. T1 corresponds to the tetramerization domain.

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