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How Lipids Contribute to Ion Channel Function, a Fat Perspective on Direct and Indirect Interactions

Julio F. Cordero-Morales[1] and **Valeria Vásquez**[1,*]

[1]Department of Physiology, University of Tennessee Health Science Center, Memphis, TN 38163, USA

Abstract

Membrane lipid composition and remodeling influence the function of ion channels. Polyunsaturated fatty acids (PUFAs) and their derivatives modulate ion channel function; whether this effect occurs directly by binding to the protein or indirectly through alteration of membranes' mechanical properties has been difficult to distinguish. There are a large number of studies addressing the effect of fatty acids; recent structural and functional analyses have identified binding sites and provided further evidence for the role of the plasma membrane in ion channel function. Here, we review cation channels that do not share a common topology or lipid-binding signature sequence, but for which there are recent compelling data that support both direct and indirect modulation by PUFAs or their derivatives.

Introduction

Biological membranes are very heterogeneous, not only in composition but also in spatial and temporal distribution [1]. They carry out multiple physiological roles, including acting as a physical barrier for ions and solutes, regulating membrane protein function, and mediating signal transmission. Singer and Nicolson proposed the fluid mosaic model 45 years ago to describe the structure of cell membranes [2]. Even though our view of biological membranes has not stood still since 1972, the model has aged considerably well. New fundamental concepts have been established to further understand the dynamic relationships between membranes and the proteins embedded in them [3]. For instance, the arrangement between membrane proteins and the lipid bilayer allows communication in two directions: one in which the lipid composition influences protein function and the other in which proteins perturb the surrounding bilayer while undergoing conformational changes [4]. Polyunsaturated fatty acids (PUFAs) are among the membrane lipid components that dynamically regulate membrane protein function. PUFAs are essential molecules that

*Corresponding author: Valeria Vásquez, Ph.D., vvasquez@uthsc.edu, Translational Science Research Building., 71 S. Manassas St., TSRB, Rm. 330J, Memphis, TN 38163, Ph.: (901)448-7223.
Julio Cordero-Morales, Ph.D., jcordero@uthsc.edu, Translational Science Research Building., 71 S. Manassas St., TSRB, Rm. 330K,Memphis, TN 38163, Ph.: (901)448-8206

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regulate gene expression, receptor signaling, and plasma membrane remodeling [5]. Notably, membranes containing different levels of PUFAs feature distinct elastic properties [6,7]. PUFAs occur esterified or as free fatty acids cleaved from the plasma membrane by phospholipases (PL: A_1, A_2, C, and D). Once released, PUFAs can be further metabolized [8], act as second messengers [9], interact with membrane proteins [10], and/or alter the mechanical properties of the bilayer [11-15]. Yet distinguishing between some of these modalities has been quite challenging.

The “force-from-lipids” principle [16] establishes that changes in bilayer force provide the energy that is needed to drive or facilitate conformational rearrangements underlying ion channel opening and closing (i.e., gating). This principle was first demonstrated 30 years ago when the purified bacterial mechanosensitive channel of large conductance (MscL) remained mechanosensitive even after reconstitution into pure bilayers [17]. However, the force-from-lipids effect also applies to other families of ion channels. Importantly, recent structure-function studies have demonstrated that lipids could also contribute to channel gating via direct lipid-protein interaction. As the direct effect of PUFAs on voltage-gated Na^+, K^+, and Ca^{2+} channels has been reviewed elsewhere [10], we will focus on other cation channels (Table 1) that do not necessarily share a common topology or PUFA-binding signature sequence, such as: glutamate receptors (N-methyl-D-aspartate receptor, NMDA), transient receptor potential (TRP) channels, mechanotransduction channel complexes, pentameric ligand-gated ion channels (pLGICs), and Ca^{2+}-activated large-conductance K^+ (BK) channels.

Ion channels whose function are influenced by the mechanical properties of the membrane

NMDA receptors and membrane tension

NMDA receptors are glutamategated ion channels crucial for neuronal communication, synaptic plasticity, and cognitive functions [18]. Nearly 25 years ago, it was shown in cultured neurons that NMDA receptor currents are potentiated by arachidonic acid (AA) [19], docosahexaenoic acid (DHA) [20], and osmotic pressure [21], but inhibited by lysophospholipids (LPLs) [22]. Interestingly, mutagenesis studies ruled out the direct interaction between AA or LPL and the putative NMDA receptor fatty acid binding domain [22]. Still, after dismissing a direct interaction between fat molecules and the channel, it was unknown whether the receptors' gating properties responded to changes in membrane tension due to the incorporation of fatty acids and LPL. Following a reductionist approach of reconstituting purified channels into liposomes, Kloda and colleagues demonstrated that NMDA receptor function is enhanced by increasing the membrane lateral tension with negative pressure or AA incorporation [23]. Thanks to the ensemble of *ex vivo* and *in vitro* experiments, it is now recognized that AA modulates NMDA receptor gating by changes in bilayer mechanical properties rather than by specific protein-binding events.

Light-sensitive TRP and TRP-like channels and phospholipid hydrolysis

Phototransduction in *Drosophila melanogaster* is mediated by phospholipase C (PLC) and the subsequent activation of two distinct ion channels, TRP and TRP-like (L) [24]. For many

years, the leading hypothesis was that PLC-mediated hydrolysis of PIP_2 yielded the second messengers diacylglycerol and IP_3, and a proton that gated these channels [16]. This natural assumption was challenged by the remarkable finding from Hardie and Franze [12,25] in which PIP_2 depletion evokes changes in the mechanical properties of the membrane that in turn activates TRP and TRPL channels [24] (Figure 1a). Furthermore, increasing lipid crowding with cationic amphiphiles inhibited the photoreceptor light responses, suggesting the membrane as a key modulator of channel gating. These results were also supported by experiments in which manipulating the fly's diet (e.g., food without PUFAs) to increase plasma membrane stiffness slowed down light-induced responses [26]. The current model highlights the contribution of the membrane by supporting the idea that reduction in area, volume, and phospholipid crowding following PIP_2 hydrolysis ultimately favors the protonation of previously buried sites in TRP and TRPL channels, which in turn promote channel gating [24].

C. elegans mechanoreceptor complex and AA-containing phospholipids

Mechanoelectrical transduction in *C. elegans* touch receptor neurons (TRNs) relies on at least 12 MEC proteins (MEC stands for proteins that when mutated confer mechanosensory abnormal phenotypes), including ion channels from the DEG/ENaC/ASIC family (MEC-4 and MEC-10) [27]. Recently, AA-containing phospholipids were shown to enhance the function of this multiprotein complex in the mechanical response of TRNs *in vivo* [14]. By examining the touch-elicited behavior of worms genetically unable to generate PUFAs, Vásquez *et al.* established that AA exerts its effect on mechanoelectrical transduction by influencing the viscoelastic properties of the plasma membrane rather than acting as a signaling molecule [14]. This was demonstrated by pulling membrane nanotubes with an atomic force microscopy (AFM) cantilever from the plasma membrane of native TRNs or TRNs genetically depleted of long PUFAs. In this context, one could imagine that the response of neurons to mechanical stimuli might be modulated by the presence of polyunsaturated bonds in the lipid acyl chains, creating a distinctive membrane environment that enhances the function of mechanoelectrical transduction channel complexes.

TRP vanilloid 4 and fatty acids

The TRP vanilloid 4 (TRPV4) channel contributes to intracellular Ca^{2+} homeostasis and is essential in mediating various physiological (e.g., vascular tone) and pathological conditions (e.g., neuromuscular diseases) [28]. TRPV4 is a polymodal ion channel activated by thermal, osmotic, and chemical stimuli [28]. Furthermore, ω-6 PUFAs, such as AA and its epoxyeicosatrienoic acid metabolites, have been shown to activate TRPV4 downstream of cell swelling [29,30]. Alternatively, it has been recently demonstrated that TRPV4 function greatly relies on the membrane environment. Plasma membranes enriched with ω-3 PUFA derivatives enhance TRPV4 activity when natively or transgenically expressed in human endothelial cells or *C. elegans* nociceptor neurons, respectively [15] (Figure 1b). Notably, among the fatty acids tested, the ω-3 eicosanoid derivative 17,18-EEQ (epoxyeicosatetraenoic acid) displayed the largest influence on TRPV4 activity, as well as in membrane fluidity, bending stiffness, and membrane structural disorder, as determined by differential scanning calorimetry and AFM [15]. The experimental results of Caires *et al.*

support the notion that ω-3 PUFA derivatives enhance channel function mainly by altering membrane mechanics rather than through a direct activation mechanism.

Ion channels whose functions are modulated by direct lipid-protein interactions

pLGICs and DHA

The nicotinic acetylcholine receptor (nAChR) from *Torpedo californica*'s electric organ is the archetypal ion channel of the pLGIC superfamily. Members of this family are responsible for fast intercellular communication at neuromuscular junctions in response to endogenous neurotransmitters [31]. Although the nAChR is a ligand-gated ion channel, its activation and desensitization rates are modulated by lipid composition [32]. Of particular importance is DHA, an ω-3 fatty acid, enriched in synaptic plasma membranes, that enhances neurotransmission [33]. Whether this fatty acid binds directly to pLGICs to alter their function was unknown until recently. Basak and colleagues determined the atomic resolution structure of a prokaryotic pLGIC (a proton-activated channel from the cyanobacterium *Gloeobacter violaceus*; GLIC) in the presence of DHA [34]. The crystal structure revealed a DHA molecule bound to the channel periphery (M4 transmembrane segment) interacting with Arg118 at the Cys-loop (in the extracellular domain; Figure 1c). Notably, DHA has the same effect enhancing GLIC desensitization rate as observed in the metazoan counterparts [35]. The interface between the transmembrane domain and the Cys-loop has been previously demonstrated to control desensitization in pLGICs [36]. Importantly, mutagenesis of GLIC R118A significantly reduced the effect of DHA on desensitization (Figure 1c, bottom). Although these results do not rule out that pLGIC gating may be also modified by the changes that free fatty acids exert on the bilayer elastic properties [11], they provide direct evidence that DHA binds to and alters the function of a pLGIC family member.

BK channels, DHA, and leukotrienes

BK channels are activated by transmembrane voltage and micromolar concentrations of Ca^{2+} [37]. These channels regulate excitability by translating local cytosolic Ca^{2+} increases into cell repolarization, a prominent feature for vascular tone and neurotransmission. Their function is significantly regulated by alternative splicing of a single gene (KCNMA1 in mammals) and other transcriptional and post-translational mechanisms, as well as association with auxiliary subunits (e.g., β1, β2, β3, and β4) [37]. A few years ago, Hoshi and colleagues determined that DHA also stimulates BK channels at nanomolar concentrations without requiring voltage activation or Ca^{2+} binding [38]. This effect on function was enhanced when BK channels were co-expressed with β1 or β4 subunits [39]. Notably, experimental evidence indicates that the effect of DHA on the BK-β1 channel complex is direct. For instance, mutagenesis of residues at the S6 helix of the BK channel (near the intracellular end of the conduction pathway, Tyr318 [40]) and the N-terminus of the β1 subunit (Arg11 and Cys18 [39]) abolished the effect of DHA on channel function (Figure 1d). Likewise, manipulation of PUFA derivatives and incorporation of unnatural amino acids led to the conclusion that the carboxylate group of DHA forms an ion-dipole

bond with Tyr318 in BK [40]. These results support a model in which the effect of DHA on the BK-β1 channel complex function is mainly due to direct protein complex-fatty acid interactions.

Leukotrienes (LTs) are inflammatory eicosanoids derived from the oxidation of AA. It turns out that only LTB4, but no other LTs, enhances BK channel function at nanomolar concentrations when in complex with the β1 auxiliary subunit [41]. However, the mechanism seems to be different from the one depicted for DHA; LTB4 binds another region of the β1 subunit and requires an optimal Ca^{2+} concentration to exert its activatory effect. Combining computational docking experiments with site-directed mutagenesis, Bukiya and colleagues determined that LTB4 increases BK activity by binding to a cholane steroid-sensing site formed by residues Thr169, Ala176, and Lys179 in the second transmembrane segment of the β1 subunit [42]. Although DHA and LTB4 specifically interact with and enhance the function of the BK-β1 channel complex, it is important to note that membrane stretch also enhances the activation of BK channels expressed in vascular smooth muscle and HEK293 cells [43]. This underlines the supposition that changes in the mechanical properties of the membrane could also influence channel function, regardless of the direct interactions that the protein might have with specific fat molecules.

TRPV1, lysophosphatidic acid, and anandamide

The TRP vanilloid 1 (TRPV1) channel is an essential component of the cellular mechanism through which noxious stimuli evoke pain [44]. TRPV1 is a polymodal channel activated by heat, capsaicin, toxins, protons, and bioactive lipids [44]. Polymodal ion channels integrate many signals acting downstream of several enzymatic cascades. Hence, it is challenging to determine which stimuli act directly or indirectly on channel function. Here, we have chosen a couple of examples for which there is evidence pointing towards a direct interaction between TRPV1 and the bioactive lipids that regulate its function. For instance, lysophosphatidic acid (LPA) is a lipid metabolite – composed of a phosphate, a glycerol, and a fatty acid [45] – involved in the development of neuropathic pain [46]. Although LPA is best known for its role in activating G-protein-coupled receptors [47], Nieto-Posadas and colleagues showed that LPA activates TRPV1, as it elicits current magnitudes comparable to those obtained with the bona fide TRPV1 activator capsaicin [48,49]. Importantly, substitution of Lys710 at the C-terminal domain of the channel (Figure 1e) with neutral or negatively charged residues severely impairs the effect of LPA on binding as well as on channel function. These results provide strong evidence that TRPV1 is directly activated by LPA.

Anandamide, an endogenous metabolite derived from the non-oxidative metabolism of AA, activates TRPV1 on primary sensory neurons [50]. Even though anandamide modifies the membrane bilayer elastic properties [51], Jordt and Julius [52] determined that anandamide interacts with the TRPV1 vanilloid-binding pocket lined by residues Tyr511, Met547, and Thr550 [53]. Remarkably, mutant Y511A does not respond to anandamide or capsaicin, while keeping normal TRPV1 heat- and proton-evoked responses [52]. Later, using a reconstituted proteoliposome system, Cao and colleagues demonstrated that anandamide activation does not require other proteins or second messengers to evoke TRPV1 ionic

currents [54]. We have previously reasoned here that direct binding does not rule out the influence that the membrane might have over channel function. However, there is compelling evidence to suggest that TRPV1 function is not modulated by membrane fluidity and/or curvature, since thermal activation does not change in cholesterol-containing membranes or when LPL is perfused to the membrane patch [54]. Moreover, capsaicin dose-response profiles of transgenic *C. elegans* expressing TRPV1 are indistinguishable between control worms and worms genetically depleted of long PUFAs [15,55]. Since it has been established that PUFA content alters the fluidity and bending stiffness of the bilayer [14], these results support the idea that TRPV1 function is not considerably modulated by the mechanical properties of the membrane.

Perspectives

The notion that ion channels only reside on a passive membrane is superseded by the fact that ion permeation relies on a dynamic cellular machine composed of both membrane proteins and lipids. However, identifying and determining the precise mechanism(s) by which lipids modulate (e.g., activate, enhance, desensitize, etc.) ion channel gating is a challenging task. For most of the ion channels reviewed here (Table 1), more than one experimental approach and laboratory were needed to establish direct and/or indirect protein-lipid interactions. Since these non-covalent interactions might not occur outside of the membrane environment and/or survive purification procedures, new approaches are required to determine their role in modulating ion channel gating. Of particular importance are nanodiscs, which are discoidal lipid bilayers stabilized by membrane scaffold proteins used to preserve the structure and function of recalcitrant membrane proteins [56,57]. New high-resolution structures of channels modulated by fatty acids in nanodiscs will provide definitive answers about this bipartite mechanism. Interestingly, new developments in mass spectrometry-based approaches have allowed quantification of lipid binding selectivity of some prokaryotic ion channels [58,59], which we hope will extend to mammalian receptors. Even if one could experimentally establish that a given ion channel is regulated by fatty acids and/or the membrane, it remains to be determined how impactful these are interactions *in vivo*.

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Highlights

- Fatty acids alter membrane mechanics and modify ion channel function.
- Fatty acids directly interact with ion channels and regulate their function.
- Structural studies reveal specific interactions between fatty acids and ion channels.

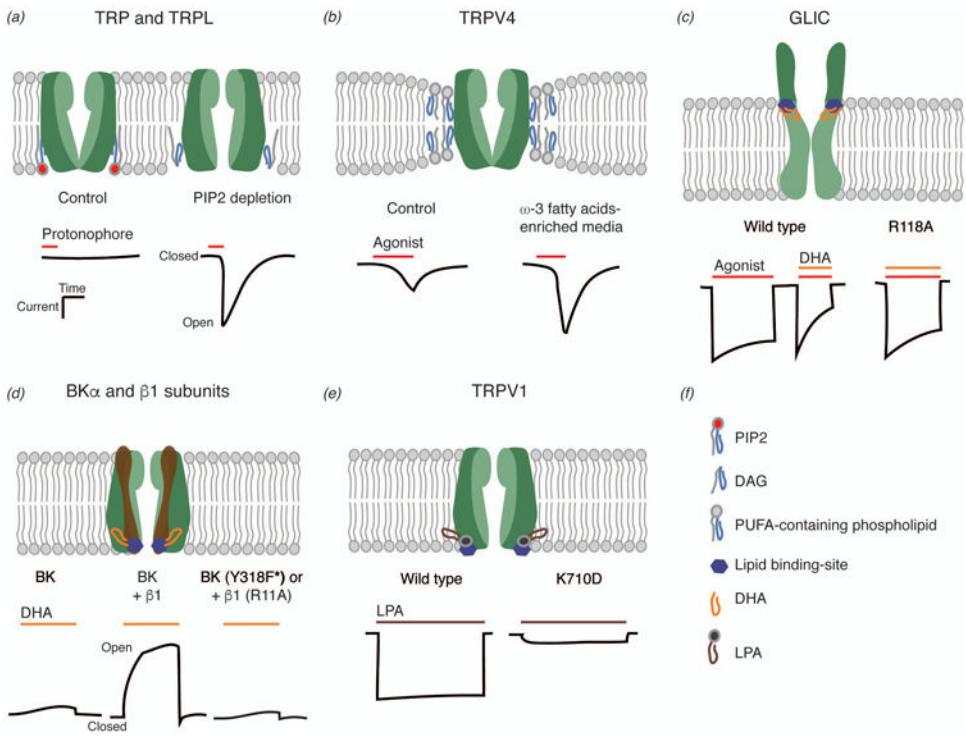

Figure 1.

Mechanisms underlying ion channel regulation by lipids. (a) Light-sensitive TRP and TRP-like(L) channels. (b) Transient receptor potential cation channel subfamily V member 4 (TRPV4). (c) Prokaryotic pentameric ligand-gated ion channel from the cyanobacterium *Gloeobacter violaceus* (GLIC). (d) Ca^{2+}-activated large-conductance K^+ (BK) channel (α) and auxiliary subunit (β1). F*: phenylalanine-based unnatural amino acid residue. (e) Transient receptor potential cation channel subfamily V member 1 (TRPV1). (f) Schematic representation of phosphatidylinositol 4,5-bisphosphate (PIP_2), diacylglycerol (DAG), polyunsaturated fatty acids (PUFAs)-containing phospholipids, docosahexaenoic acid (DHA), and lysophosphatidic acid (LPA).

Table 1
Ion channels modulated directly and/or indirectly by lipids

Type of Interaction	Ion channel	Lipid	Effect on function	Reference
Indirect	NMDA	AA	Potentiation	[23]
	TRP and TRPL	PIP_2 depletion	Activation	[12,25]
	C. elegans mechanoreceptor complex	AA-containing phospholipids	Enhance activation	[14]
	TRPV4	EEQ- containing phospholipids	Enhance activation	[15]
Direct	pLGIC	DHA	Enhance desensitization	[34,35]
	BK	DHA	Activation	[38-40]
	BK	LTB4	Enhance activation	[41]
	TRPV1	LPA	Activation	[48,49]
	TRPV1	Anandamide	Activation	[50,52,54]