Biochimica et Biophysica Acta xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbalip

Review

Phosphoinositides regulate ion channels ☆

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ARTICLE INFO

Article history:
Received 3 July 2014
Received in revised form 9 September 2014
Accepted 10 September 2014
Available online xxxx

Keywords:
Phosphatidylinositol 4,5-bisphosphate
Phospholipase C (PLC)
G-protein coupled receptor (GPCR)
Potassium channel
Calcium channel
Transient receptor potential channel (TRP channel)

ABSTRACT

Phosphoinositides serve as signature motifs for different cellular membranes and often are required for the function of membrane proteins. Here, we summarize clear evidence supporting the concept that many ion channels are regulated by membrane phosphoinositides. We describe tools used to test their dependence on phosphoinositides, especially phosphatidylinositol 4,5-bisphosphate, and consider mechanisms and biological meanings of phosphoinositide regulation of ion channels. This lipid regulation can underlie changes of channel activity and electrical excitability in response to receptors. Since different intracellular membranes have different lipid compositions, the activity of ion channels still in transit towards their final destination membrane may be suppressed until they reach an optimal lipid environment. This article is part of a Special Issue entitled Phosphoinositides.

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1. Introduction

This article considers some key points in the regulation of ion channels by phospholipids. The prescient original concept, from the work of Hilgemann and Ball [1], was that ion channels in the plasma membrane interact with and need local membrane phosphoinositide phospholipids for proper function. We know by now that phosphoinositides do regulate a large number of ion channels. The major themes of our essay are as follows: Definitive evidence and a fairly complete story of ion channel regulation exist for a select few exemplar channels. Partial evidence and a suggestive picture exist for many more, and negative evidence or no positive evidence exists for the remainder. Some channels may not be sensitive to phosphoinositides at all. Some ion channels have an obligate requirement for one species of phosphoinositide, whereas others may accept a broader range of phosphoinositides or anionic lipids. Some channels do not function without their preferred lipid and others function differently with and without that lipid. Some channels interact with lipid partners so strongly (high affinity) that the binding site probably remains saturated during most physiological changes of the lipid concentration. Others bind more loosely (low affinity). For the low-affinity channels, variations of lipid levels may act as physiological signals that regulate the computational properties of neurons and the transport properties of secretory cells.

Other articles in this issue review several important properties of phosphoinositide phospholipids that we take here as given. Phosphoinositides derive by phosphorylation from the parent membrane lipid phosphatidylinositol (PI) by combinatorial phosphorylation of the 3, 4, and 5 positions of the inositol head group, so that seven phosphorylated forms exist [2,3]. The polyphosphoinositides are the most negatively charged of all membrane lipids. They are found only in the cytoplasmic leaflet of the surface membrane and of organellar membranes. All except for PI itself are relatively minority lipids (at most a few mole percent in the membrane) and can serve signaling functions. The different species of phosphoinositides have markedly different abundance in membranes of different organelles of the cell so they act like zip codes or signature motifs of those membranes (Fig. 1; [4]). They are interconverted on a second time scale by lipid kinases and lipid phosphatases at the budding and fusing steps of membrane traffic. Finally, phosphoinositides are subject to regulation by membrane receptors. For example, the signature lipid of the plasma membrane, phosphatidylinositol 4,5-bisphosphate ($PI(4,5)P_2$), can be depleted by receptor activation of phospholipase C (PLC), and a small fraction of $PI(4,5)P_2$ can be converted to the potent signal $PI(3,4,5)P_3$ by receptor activation of lipid 3-kinases [5].

2. Two hypotheses

What is regulation by lipids good for? We discuss two hypotheses diagramed in Figs. 1 and 2. We think both are correct. Ion channels are

☆ This article is part of a Special Issue entitled Phosphoinositides.

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http://dx.doi.org/10.1016/j.bbalip.2014.09.010
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large integral membrane proteins that become irreversibly imbedded in the lipid bilayer during their synthesis and assembly in the endoplasmic reticulum (ER). They remain membrane imbedded at all times as they traffic through the Golgi and usually continue onto other target membranes via transport vesicles. The vast majority of ion channels that have been studied so far are those targeted to the plasma membrane. During this traffic, integral membrane proteins experience the different signature lipids of each cellular compartment through which they pass. One major hypothesis, regulation in space, has been tested only in very limited ways: It proposes that the phospholipid composition of each compartment controls the activity of channels in transit so that until they arrive at the target membrane, channels may be turned off or altered in function in an adaptive manner [6]. This bold cell biological hypothesis might be broadly relevant to many other integral membrane proteins whether transporters, receptors, enzymes, or ion channels.

A second hypothesis is regulation in time by receptors. While integral membrane proteins like ion channels are residing in the plasma membrane, receptors coupled to PLC or to lipid 3-kinases may become activated and transiently change key membrane lipids sufficiently to modulate channel function. Thus, the electrical and ion-transport properties of the cell may be regulated dynamically by phosphoinositide signaling. As was already pointed out, such regulation in time would apply to channels that do not bind the lipids with very high affinity since the membrane concentration of lipids is likely changed by less than one order of magnitude during receptor activation of enzymes. At times, receptor-induced lipid changes may be graded and modest and their signals and effects on channels may be graded and modest.

3. Tools for study

To study such hypotheses requires tools. Ideally, we should measure the subcellular location and concentrations of the phosphoinositide species, and we should manipulate them up and down. At the same time, we need good assays of the functional changes of the regulated ion channels. Preferably, the measurements, manipulations, and functional assays could be used together in real time on living cells. Fortunately, the techniques and apparatus of patch clamp electrophysiology lend themselves nicely to approaching these ideals. Electrical recording from a cell on a microscope stage is intrinsically a real-time method with millisecond time resolution. Cell photometry or imaging with relevant multicolored fluorescent probes is easily done at the same time on the microscope, and bathing solutions with agonists and inhibitors can be changed by local perfusion, within seconds. Epifluorescence, confocal, and total internal reflection fluorescence (TIRF) microscopy are all possible.

Fluorescently labeled pleckstrin homology domains (PH domains) or other domains with binding specificity for a subset of phosphoinositides are widely used molecular tools for detecting various phosphoinositides [7,8]. The first was PH-PLCδ1-GFP, which binds selectively to the plasma membrane lipid $PI(4,5)P_2$, showing as a bright fluorescent ring around the edge of a cell in confocal microscopy [9,10]. It also recognizes inositol 1,4,5-trisphosphate. The probe translocates away from the plasma membrane if $PI(4,5)P_2$ is depleted. Other probes recognize PI(4)P, $PI(3,5)P_2$, etc. Translocation can be followed from the changes of brightness of regions of interest in confocal imaging. Alternatively, translocation of the same fluorescent probes can be studied with Förster resonance energy transfer (FRET) if a suitable FRET-pair of colors is chosen to label the PH domain and a second protein of known location. There will be FRET when they are closely apposed at the same membrane and a loss of FRET when they move apart. A common FRET pair is PH-PLCδ1-YFP and a specific membrane anchor tagged with CFP or even PH-PLCδ1-CFP itself.

A second set of tools are methods to perturb the phosphoinositides of the cell, preferably fast, specific, and compatible with living cells. Several methods manipulate exogenous or endogenous enzymes. Many of these have been outlined by De Camilli and Idevall-Hagren [11] so a short list will suffice. Fig. 2 shows a small subset of phosphoinositide metabolism that includes the enzymes of interest here. The standard biosynthesis of $PI(4,5)P_2$ proceeds from PI through PI(4)P to $PI(4,5)P_2$. PI is converted to PI(4)P by a lipid 4-kinase. PI(4)P is converted back to PI by a 4-phosphatase and into $PI(4,5)P_2$ by a PI(4)P 5-kinase. $PI(4,5)P_2$ is converted back to PI(4)P by a 5-phosphatase. $PI(4,5)P_2$ is also cleaved into diacylglycerol and IP_3 by receptor-activated PLC, mobilizing several second messengers and signaling pathways. The conventional approaches of cell biology would be overexpression of the enzyme or of a dominant-negative mutant by transfection, or knockdown by

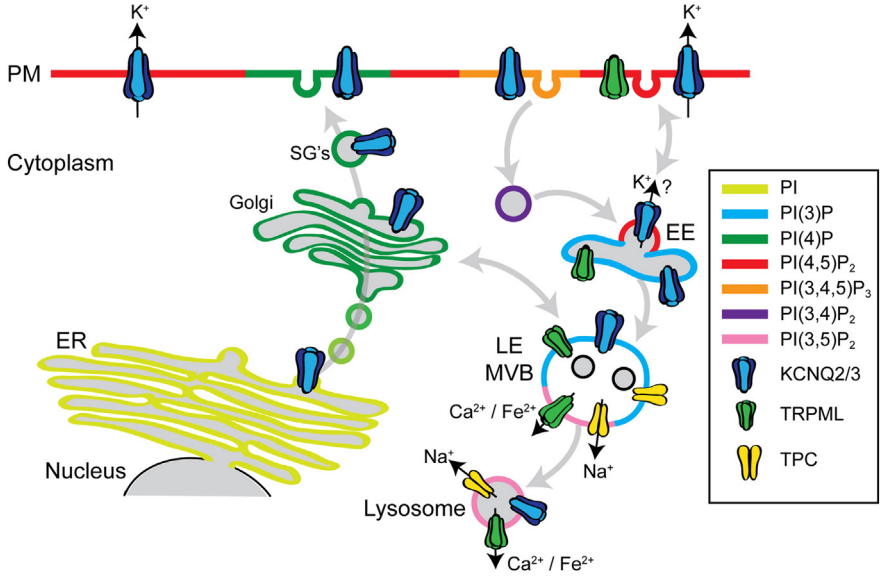

Fig. 1. Organelle phosphoinositide signature helps regulate ion channel function. Schematic representation of the predominant subcellular localization of phosphoinositide species in each organelle. $PI(4,5)P_2$ and $PI(3,4,5)P_3$ are concentrated at the plasma membrane (PM). $PI(3,4)P_2$ is found mostly in early endocytic pathways distal to the plasma membrane. PI(4)P is principally concentrated in the Golgi complex, but can also be found at the plasma membrane and secretory pathways (SGs). PI(3)P is located in early endosomes (EE) and $PI(3,5)P_2$ on late endosomal (LE), multi-vesicular body (MVB), and lysosomal compartments. PI is found in the endoplasmic reticulum (ER). Gray arrows represent the continuous flow of membrane between organelles. Note that heterotetrameric KCNQ2/3 ion channels are closed (no arrow) during trafficking and retrieval from the plasma membrane, but are open (with arrow) at the plasma membrane due to the presence of appropriate activating phosphoinositide ($PI(4,5)P_2$) and membrane voltage.

Please cite this article as: B. Hille, et al., Phosphoinositides regulate ion channels, Biochim. Biophys. Acta (2014), http://dx.doi.org/10.1016/j.bbalip.2014.09.010

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