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Review

Phosphoinositide dynamics in the postsynaptic membrane compartment: Mechanisms and experimental approach

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ABSTRACT

Phosphoinositides (PIs) are minor constituents of eukaryotic membranes that control a plethora of cellular functions through direct modulation of membrane-associated proteins and through membrane recruitment of enzymes or signaling molecules. It is well established that in neurons PIs play essential roles in the pre-synapse, especially during exocytotic neurotransmitter release and recycling of synaptic vesicles. In contrast, the physiological importance of PIs in postsynaptic membranes is far less understood. The extent and the spatiotemporal characteristics of dynamic changes in the concentrations of PIs caused by synaptic activity are largely unknown. Recent work suggests that postsynaptic PI dynamics are involved in the induction and maintenance of synaptic plasticity, but the general principles are far from clear. This review summarizes current knowledge on the relevance of PIs for postsynaptic processes, focussing on PI signaling in the control of electrical activity and synaptic plasticity. We highlight the state-of-the-art of methods to study PI dynamics and discuss recent technical improvements that should help to define the role of PIs in postsynaptic physiology.

1. Introduction

Phosphoinositides (PIs) are minor components of the cytoplasmic leaflet of all eukaryotic cellular membranes. Differential phosphorylation of phosphatidylinositol at the positions 3, 4, and 5 of the inositol head moiety results in seven distinct PI isoforms, which are present in the membranes of different organelles at different concentrations (Toker, 2002). A large body of work described PIs as signaling molecules and essential regulators of a diversity of cellular processes including membrane fusion and fission, cytoskeletal reorganization or the regulation of membrane proteins (Toker, 2002; Di Paolo and De Camilli, 2006). PIs affect cellular functions either by direct modulation of the activity of membrane-associated proteins such as ion channels and transporters or through reversible recruitment of enzymes and signaling molecules to membranes. The recruitment of proteins is mediated through (more or less specific) interaction of inositide-binding domains with different PI species. For a detailed and comprehensive review on the biology of PIs we refer to an excellent recent article by Balla (2013).

In the plasma membrane, PI(4)P and PI(4,5)P_2 are the most abundant PIs, whereas the 3-phoshorylated isoforms, PI(3,4,5)P_3 and PI(3,4)P_2, usually occur at much lower concentrations in resting cells. However, PI(3,4,5)P_3 and PI(3,4)P_2 can be up-regulated strongly in response to activation of various receptors (Balla, 2013). The concentrations of individual PI species are controlled by a complex set of specific lipid kinases, phosphatases and lipases. These enzymes are involved in homeostatically setting the resting levels of PIs; however, their regulation by a variety of signaling events enables dynamic modification of PI concentrations at different time scales (Di Paolo and De Camilli, 2006; Balla, 2013). An important and well-studied example is the cleavage of PI(4,5)P_2 by phospholipase C (PLC) downstream of the activation of G-protein-coupled receptors (GPCRs) that signal via the $G\alpha_{q/11}$ subtype of heterotrimeric G-proteins. Receptor-triggered activation of PLC can massively deplete PI(4,5)P_2 within seconds thereby producing diacylglycerol (DAG) and inositol-1,4,5-trisphosphate (IP_3) that both are important second messengers (Horowitz et al., 2005; Kadamur and Ross, 2013). Accordingly, PI(4,5)P_2 serves as precursor for signaling molecules, but because PI(4,5)P_2 in itself constitutes an important cofactor for many membrane-associated proteins (e.g. ion channels), PLC-induced PI(4,5)P_2 dynamics may directly and rapidly modulate the activity of these proteins (Suh and Hille, 2008; Falkenburger et al., 2010c).

PIs are at the heart of neuronal function, in particular of neuronal plasticity, through the modulation of synapse function and

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structure as well as electrical signaling through regulation of ion channel activity or trafficking. It is well established that PIs have a pivotal role in presynaptic function, especially during transmitter release through exocytosis of synaptic vesicles and subsequent endocytotic retrieval of membrane for recycling of synaptic vesicles. An excellent recent review covering these aspects is available (Frere et al., 2012). In contrast, the physiological relevance of PIs in postsynaptic compartments is far less understood. Recent work demonstrated that PIs are involved in maintenance of synaptic function and in activity-dependent changes of synaptic strength through postsynaptic mechanisms (reviewed in Dotti et al., 2014; Ueda, 2014), but the molecular mechanisms are largely unknown. Likewise, it is currently unknown whether physiological synaptic activity patterns affect PI concentrations in the postsynapse. Focussing on PI dynamics that released neurotransmitters exert onto postsynaptic neurons, we selectively highlight recent findings that shed light onto the role of these membrane lipids in postsynaptic signaling. Furthermore, we review technical progress that may help to obtain a coherent picture of the mechanistic role of PIs in postsynaptic physiology.

2. Modulation of neural excitability via PLC-coupled metabotropic neurotransmitter receptors

Many neurotransmitters (actually the majority of transmitters) act through metabotropic, i.e. G-protein-coupled, receptors. The postsynaptic effects include transient or long-lasting changes in the electrical properties of the postsynaptic neuron (i.e. neuromodulation), which result from the activation or shutdown of specific ion channels via a second messenger cascade (e.g. Brown et al., 2007).

Among those, many receptors are coupled to Gα proteins of the $G\alpha_{q/11}$ class, which act through activation of phospholipase Cβ (PLCβ). PLCβ in turn mediates the hydrolysis of $PI(4,5)P_2$ (Kadamur and Ross, 2013), thereby generating the two important second messengers diacylglycerol (DAG) and inositol-1,4,5-trisphosphate (IP_3). However, the activity of PLCβ can also strongly affect the concentration of its substrate, $PI(4,5)P_2$ (Horowitz et al., 2005; Nelson et al., 2008; Quinn et al., 2008; Kadamur and Ross, 2013). Because many ion channels are dependent on resting $PI(4,5)P_2$ levels for their activity (Suh and Hille, 2008; Falkenburger et al., 2010c), an obvious pathway that modulates cellular excitability is the direct regulation of ion channel activity by receptor-induced $PI(4,5)P_2$ concentration dynamics. In the following chapter, we review the evidence and experimental model systems that link transmitter-mediated channel regulation to neuronal $PI(4,5)P_2$ concentration dynamics.

In the prototypical and extensively studied example, activation of G_q-coupled muscarinic acetylcholine receptors ($M_1/M_3/M_5$) results in inhibition of a voltage-dependent K^+ current that was therefore named M (muscarinic) current (Brown and Adams, 1980). The underlying channels belong to the Kv7 (or KCNQ) family of voltage-gated K^+ channels, and are probably mostly heteromeric Kv7.2 and Kv7.3 channels in neurons (Wang et al., 1998). They mediate relatively slowly activating and non-inactivating K^+ currents and are partially active at resting or moderately depolarized membrane potentials (Biervert et al., 1998; Schroeder et al., 1998; Wang et al., 1998). Accordingly, their inhibition results in depolarization and the release of a hyperpolarizing 'brake' for repetitive action potential firing (Jentsch, 2000), thus allowing for increased action potential firing (Jentsch, 2000; Okubo et al., 2004; Yue and Yaari, 2004; Peters et al., 2005; Tzingounis and Nicoll, 2008). Consistent with the function in dampening excitation in central neurons, loss-of-function mutations of Kv7.2 and Kv7.3 channels lead to epileptic seizures in newborns (Biervert et al., 1998; Charlier et al., 1998; Singh et al., 1998). M-current inhibition and the resulting increase in excitability have been shown not only in response to activation of muscarinic receptors but for many different G_qPCRs in various types of neurons, including sympathetic (Brown and Adams, 1980; Cruzblanca et al., 1998; Ford et al., 2003, 2004; Winks et al., 2005; Zaika et al., 2006; Brown et al., 2007; Hughes et al., 2007; Linley et al., 2008; Liu et al., 2008), cortical (Constanti and Sim, 1987; Nishikawa et al., 1994; Glasgow and Chapman, 2013) and hippocampal neurons (Halliwell and Adams, 1982; Dutar and Nicoll, 1988; Shah et al., 2002; Young et al., 2005). The activity of all Kv7 isoforms strictly depends on the presence of $PI(4,5)P_2$ in the physiological concentration range, such that depletion of $PI(4,5)P_2$ to values below typical resting concentrations leads to channel closure (Suh and Hille, 2002; Zhang et al., 2003; Horowitz et al., 2005; Suh et al., 2006; Hernandez et al., 2009; Falkenburger et al., 2010a). Given the potential of PLC to deplete $PI(4,5)P_2$ downstream of G_qPCRs, G_q-coupled transmitter receptors may modulate neuronal behavior directly by inducing $PI(4,5)P_2$ dynamics.

The mechanism of neuronal M-current regulation has been analyzed most thoroughly in neurons of the superior cervical ganglion (SCG). Here, both G_q-coupled muscarinic ACh (mAChR) and bradykinin receptors, among others, suppress M-currents/Kv7 channels, which involves activity of PLCβ (Brown et al., 2007). Surprisingly, even within this single neuron type the molecular messenger causing channel closure was found to differ depending on which receptor was activated (Cruzblanca et al., 1998). In SCG neurons the activation of mAChR results in substantial depletion of $PI(4,5)P_2$ leading to channel deactivation (Gamper et al., 2004; Winks et al., 2005; Hughes et al., 2007). Similarly, inhibition of Kv7 channels through histamine (Liu et al., 2008), angiotensin (Zaika et al., 2006), luteinizing hormone releasing hormone (Ford et al., 2004), and purinergic receptors (Ford et al., 2003, 2004) was found to be mediated by PLCβ-dependent $PI(4,5)P_2$ depletion. Similar inhibition of Kv7 currents through mechanisms involving PLC and $PI(4,5)P_2$ depletion has been shown in dorsal root ganglia (Linley et al., 2008).

In contrast, in SCG neurons M-channel inhibition by bradykinin and purinergic receptors is most probably not mediated by $PI(4,5)P_2$ depletion (Cruzblanca et al., 1998; Bofill-Cardona et al., 2000; Brown et al., 2007; Hernandez et al., 2008). Stimulation of the bradykinin receptor does not induce strong depletion of $PI(4,5)P_2$ (Gamper et al., 2004; Winks et al., 2005; Hughes et al., 2007), which is supported by the observation that $PI(4,5)P_2$-sensitive N-type calcium channels were only inhibited by activation of mAChRs but not by bradykinin receptors (Gamper et al., 2004). Instead, inhibition of Kv7 channels through bradykinin receptors in SCG neurons is mediated by increased Ca^{2+}, which acts on the channels via calmodulin (Cruzblanca et al., 1998; Gamper et al., 2005; Hernandez et al., 2008; Kosenko et al., 2012).

Despite these different pathways, mAChR and Bradykin receptors induce similar degrees of PLCβ activity (Gamper et al., 2004; Winks et al., 2005; Hughes et al., 2007). The difference in the intracellular signals that originate from activity of each receptor type suggested that at least in SCG neurons these receptors reside in distinct microdomains, where particularly the association with ER compartments determines the degree of $PI(4,5)P_2$ depletion and the Ca^{2+} signal (Delmas et al., 2002; Brown et al., 2007; Hernandez et al., 2008). Thus, tight association of the bradykinin receptors with IP_3 receptors allows for IP_3-mediated rise of $[Ca^{2+}]$, which on the one hand appears to stimulate $PI(4,5)P_2$ synthesis to compensate for consumption by PLCβ, effectively preventing substantial changes in $PI(4,5)P_2$ concentration (Gamper et al., 2004), and on the other hand directly inhibits Kv7 channels (Cruzblanca et al., 1998; Gamper et al., 2005; Hernandez et al., 2008; Kosenko et al., 2012). In contrast, muscarinic receptors lack the spatial proximity