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Phosphoinositide signaling in somatosensory neurons

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ABSTRACT

Somatosensory neurons of the dorsal root ganglia (DRG) and trigeminal ganglia (TG) are responsible for detecting thermal and tactile stimuli. They are also the primary neurons mediating pain and itch. A large number of cell surface receptors in these neurons couple to phospholipase C (PLC) enzymes leading to the hydrolysis of phosphatidylinositol 4,5-bisphosphate [$PI(4,5)P_2$] and the generation of downstream signaling molecules. These neurons also express many different ion channels, several of which are regulated by phosphoinositides. This review will summarize the knowledge on phosphoinositide signaling in DRG neurons, with special focus on effects on sensory and other ion channels.

Contents

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1. Introduction

The primary somatosensory neurons that mediate temperature and touch sensation as well as detect painful stimuli are dorsal root ganglion (DRG) and trigeminal ganglion (TG) neurons. They are pseudounipolar cells; their peripheral processes conduct nerve impulses from the skin or mucous membranes, and the shorter central processes convey information to the central nervous system. The nerve fibers the axons of DRG neurons form are classically categorized by diameter and conduction velocity, to unmyelinated C-fibers with the slowest conduction velocity, associated with temperature and pain detection, myelinated Aδ fibers associated with pain and temperature sensation, Aβ fibers associated with mechanosensation, and Aα sensory fibers that convey information from proprioceptors.

Intense mechanical and thermal stimuli evoke pain; this acute nociceptive pain is a major defense mechanism against tissue damage. Pain can become chronic via two general mechanisms: chronic inflammation sensitizes the pain pathway to otherwise non-painful stimuli, and either physical or chemical nerve damage leads to neuropathic pain. Chronic pain is a major unsolved medical problem, and has been a significant driving force behind research on this field (Basbaum et al., 2009). Skin diseases, and exposure of the skin to irritants often induce itch, which is also detected by DRG neurons, and also a significant medical problem (Bautista et al., 2014).

The cell bodies of DRG and TG neurons are relatively easy to isolate, and they survive well in cell culture, thus they are amenable to electrophysiological characterization using the patch clamp technique. The peripheral nerve endings, where physiological sensation actually happens, are not accessible for patch clamping. While nerve impulses can be detected that arise from these nerve termini, using for example the skin-nerve preparation (Zimmermann et al., 2009), these composite nerve signals do not convey sufficient information on the contribution of individual ion channel types. Most of our knowledge about ion channels in sensory neurons comes from electrophysiological characterization of cell bodies, and we assume that a similar set of ion channels are found in the nerve termini. This assumption has been confirmed by many genetic knockout studies, where deletion of ion channels described in the cell body, had the expected sensory phenotype, indicating that the ion channel is also present in the peripheral termini.

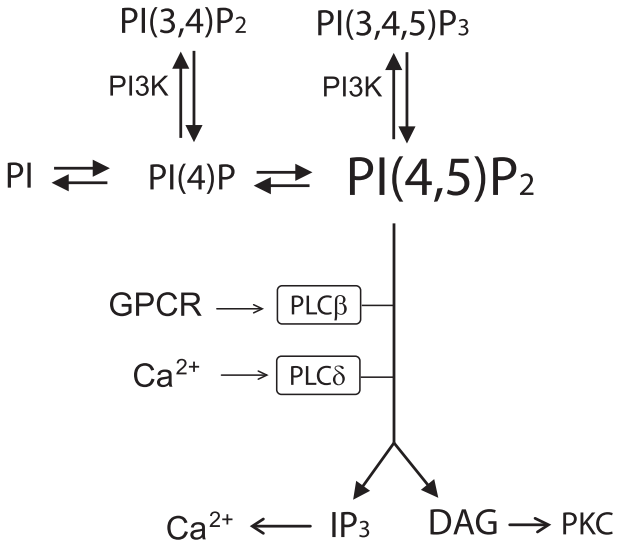

Fig. 1. Phosphoinositide metabolism.

Sensory neurons express a large number of G-protein coupled receptors (GPCR-s), many of which couple to phospholipase C (PLC) enzymes via G_q proteins (Stone and Molliver, 2009). The best understood primary function of these receptors is sensitization of the sensory system upon inflammation (Linley et al., 2010). This sensitization is responsible for the well-known phenomenon of thermal hyperalgesia and mechanical allodynia, the increased sensitivity to heat, cold and mechanical stimuli during inflammation (Linley et al., 2010). G_q-coupled GPCR-s also play important roles in itch (Liu and Dong, 2015). In addition, PLC enzymes may also be stimulated by Ca^{2+} influx via ion channels (Rohacs et al., 2005).

This review will describe the various ion channels found in sensory DRG and TG neurons, and will focus on how phosphoinositide signaling influences them. We will discuss direct regulation of ion channels by phosphatidylinositol 4,5-bisphospate [$PI(4,5)P_2$], and the consequences of changes in phosphoinositide levels on ion channel activity. We will also summarize the effects of downstream signaling after PLC activation on neuronal ion channels.

DRG and TG neurons are very diverse. There is no single neuron in which all of the ion channels described below would be expressed. Various categorizations of peripheral sensory neurons have been proposed (Basbaum et al., 2009), detailed description of which is beyond the scope of this review. The most recent one of these, based on unbiased principle component analysis of RNA sequencing data from a large number of individual neurons, divided mouse DRG neurons to 11 neuronal subpopulations (Usoskin et al., 2015). The 5 neurofilament positive subpopulations correspond to myelinated low threshold mechanoreceptors (NF1-3) and myelinated proprioceptors (NF4-5), the 3 non-peptidergic neuron populations (NP1-3) correspond to non-myelinated nociceptors and neurons responsible for itch, and the 2 peptidergic subpopulations correspond to non-myelinated (PEP1) and lightly myelinated (PEP2) peptidergic thermosensitive nociceptors. A larger tyrosine hydroxylase positive population (TH) corresponded to non-myelinated low-threshold mechanoceptors (Li et al., 2011). The vast majority of GPCR-s and sensory ion channels discussed in this review are predominantly expressed in the NP and PEP groups, and to some extent in the TH group described in (Usoskin et al., 2015).

2. PLC-coupled GPCR signaling in sensory neurons

Cell surface receptors that couple to G_q/G_{11} proteins, activate PLCβ enzymes that hydrolyze $PI(4,5)P_2$ into the two classical second messengers: inositol 1,4,5-trisphosphate (IP_3), which releases Ca^{2+} from intracellular stores via binding to the IP_3 receptor (Mikoshiba, 2015) and diacylglycerol (DAG), which activates Protein Kinase C (PKC) (Fig. 1). Consistent with the role of this pathway in pain sensitization, nociceptor specific dual deletion of G_q and G_{11} reduced hypersensitivity in both inflammatory and neuropathic pain models (Tappe-Theodor et al., 2012). On the RNA level, the highest expressing PLCβ isoform in DRG neurons is PLCβ3 (Thakur et al., 2014). Genetic deletion of this enzyme significantly reduced histamine mediated itch (Han et al., 2006). Ca^{2+} signals induced by histamine in DRG neurons were eliminated in PLCβ3$^{-/-}$ mice, but responses to other agonists, such as bradykinin or UTP were intact, showing the presence and importance of other PLCβ isoforms. PLCβ isoforms may also localize to the nucleus in brain cortical neurons, where they play distinct roles from their effects at the plasma membrane (Garcia del Cano et al., 2014), but this area of research is largely unexplored in peripheral sensory neurons.

DRG neurons express a variety of GPCR-s that are activated by inflammatory mediators, and many of these receptors couple to G_q and PLCβ enzymes (Stone and Molliver, 2009). GPCR-s that activate PLC in DRG neurons include bradykinin B2 receptors, purinergic P2Y receptors, chemokine receptors, prostaglandin receptors (EP1), lysophosphatidic acid (LPA) receptors and proteinase-activated (PAR) receptors. As mentioned earlier, the best-known function of these receptors in DRG neurons is to sensitize the pain pathway. Examples for this sensitization will be discussed throughout this review.

Some of the highest expressing G_q coupled receptors in DRG neurons are the members of the Mas1-Related G protein-coupled receptor (Mrgpr) family (Liu and Dong, 2015). While the endogenous ligands for several of these receptors are not yet known, Mrgpr-s are involved in histamine independent itch (Liu and Dong, 2015). MrgprA3 was shown to be activated by chloroquine, an antimalarial drug that cause itch as a side effect (Liu et al., 2009). It was shown that chloroquine-induced itch involves the activation of TRPA1 channels (Wilson et al., 2011). MrgprD on the other hand was found to be activated by β-alanine, also known to induce itch (Liu et al., 2012). Mrgprd activation by β-alanine was also shown to inhibit KCNQ channels, which could also contribute to increased neuronal excitability (Crozier et al., 2007).

3. Changes in phosphoinositide levels upon GPCR activation

While stimulation of overexpressed G_q-coupled receptors usually induces clear reduction in phosphoinositide levels (Falkenburger et al., 2010; Borbiro et al., 2015), stimulation of endogenous receptors in different cell types show highly variable responses in decrease of $PI(4,5)P_2$ (van der Wal et al., 2001). To generate a clear IP_3-induced Ca^{2+} signal, hydrolysis of a relatively small fraction of $PI(4,5)P_2$ is sufficient and $PI(4,5)P_2$ levels do not necessarily have to decrease substantially during receptor stimulation. Surprisingly little is known on phosphoinositide dynamics in response to stimulating endogenous G_q coupled receptors in peripheral somatosensory neurons. It was proposed that bradykinin, while clearly activates PLC, does not decrease $PI(4,5)P_2$ levels in rat DRG neurons (Liu et al., 2010). The authors found that bradykinin induced the translocation of the GFP-tagged PLCδ1-PH domain from the plasma membrane to the cytoplasm, a phenomenon often interpreted as depletion of $PI(4,5)P_2$. The PLCδ1-PH domain binds to $PI(4,5)P_2$ with high affinity and specificity, but it also binds IP_3, the product of the activation of PLC (Hirose et al., 1999). Thus it is debated how much $PI(4,5)P_2$ depletion and displacement by IP_3 contributes to the translocation of this construct (van der Wal et al., 2001; Xu et al., 2003; Szentpetery et al., 2009). When using the GFP-tagged phosphoinositide binding domain of the tubby protein, which does not bind IP_3, (Quinn et al., 2008)

bradykinin did not induce significant translocation (Liu et al., 2010), indicating that bradykinin may not induce a substantial decrease in $PI(4,5)P_2$ levels. An earlier report found that stimulation of Protease activated PAR-2 receptors induce the translocation of PLCδ1-PH domain from the plasma membrane to the cytoplasm, indicating PLC activation and potential decrease in $PI(4,5)P_2$ levels (Linley et al., 2008).

In our work, we found that using the same tubby-GFP construct used by Liu et al., bradykinin evoked a small but significant decrease in $PI(4,5)P_2$ levels in mouse DRG neurons (Lukacs et al., 2013b). This decrease was markedly smaller than that induced by capsaicin, which activates a Ca^{2+} sensitive PLC, most likely a PLCδ isoform by stimulating Ca^{2+} influx via TRPV1 channels, see next paragraph. Bradykinin, unlike capsaicin, did not induce any decrease in PI(4)P levels, as detected by a fluorescence based PI(4)P sensor (Lukacs et al., 2013b). While there is some quantitative discrepancy between the two papers, they agree that bradykinin activated PLC, but it only induced a small (or no) decrease in $PI(4,5)P_2$ levels (Liu et al., 2010; Lukacs et al., 2013b). Even though DRG neurons express a large number of G_q coupled receptors, to our knowledge, the effects of other endogenous receptors on phosphoinositide dynamics have not been tested so far.

4. Activation of PLC by Ca^{2+} influx

As mentioned before, activation of TRPV1 channels by capsaicin in DRG neurons lead to a robust depletion of $PI(4,5)P_2$ and PI(4)P in a Ca^{2+} influx dependent manner (Lukacs et al., 2013b). Capsaicin also induced the formation of IP_3, showing that the mechanism is PLC activation (Lukacs et al., 2007). As we will discuss later, PLC-mediated phosphoinositide depletion plays an important role in Ca^{2+}-dependent desensitization of TRPV1 (Lukacs et al., 2013b). Ca^{2+} influx via TRPM8 was also shown to deplete $PI(4,5)P_2$ (Rohacs et al., 2005; Daniels et al., 2009) in a Ca^{2+} dependent manner, accompanied by the formation of IP_3 (Yudin et al., 2011). Similar to TRPV1, Ca^{2+} -induced PLC activation plays a role desensitization of TRPM8 (Yudin and Rohacs, 2011), see also later. Depolarization of DRG neurons by 20 mM potassium chloride also induced depletion of $PI(4,5)P_2$ and PI(4)P in DRG neurons, even though to a lesser extent than capsaicin (Lukacs et al., 2013b). The Ca^{2+} signal evoked by potassium chloride was also smaller than that induced by capsaicin, when measured with a low affinity Ca^{2+} sensitive dye (Lukacs et al., 2013b).

There are 13 isoforms of PLC in the human genome (Fukami et al., 2010). GPCRs activate PLCβ1-4 via Gαq or Gβγ, and Receptor Tyrosine Kinases activate PLCγ1 and PLCγ2. While all PLC isoforms require some Ca^{2+} for activity, PLCδ-s, but not PLCβs or PLCγs, were shown to be activated by Ca^{2+} alone (Allen et al., 1997). The more recently discovered PLCη1 and PLCη2 (Cockcroft, 2006), as well as the sperm specific PLCζ are also highly Ca^{2+} sensitive, but these isoforms are not expressed in DRG neurons (Lukacs et al., 2013b; Thakur et al., 2014). PLCε RNA can be detected in whole DRG-s, but it is essentially not expressed in DRG neurons (Thakur et al., 2014), thus the most likely isoforms to be activated by Ca^{2+} influx in DRG neurons are PLCδs. PLCδ4, at the RNA level, is expressed several fold higher in DRG neurons than the other two PLCδ isoforms PLCδ3 and PLCδ1 (Lukacs et al., 2007; Hammer et al., 2010; Gerhold et al., 2013; Thakur et al., 2014). Accordingly, capsaicin-induced desensitization of TRPV1 was reduced in PLCδ4$^{-/-}$ mice, but the effect was relatively moderate, pointing to the possible contribution of other PLC(δ) isoforms to phosphoinositide depletion.

As mentioned earlier, activation of TRPV1 by capsaicin induced a much larger depletion of phosphoinositides in DRG neurons than stimulation of bradykinin receptors. Bradykinin receptor expression in adult mouse DRG neurons is quite low, while TRPV1 expresses at quite high levels (Thakur et al., 2014) thus it can be argued that the difference is due to low expression levels of the GPCR. Interestingly however, TRPV1 activation was also more efficient in phosphoinositide depletion than GPCR activation when TRPV1 was co-expressed with muscarinic M1 receptors and phosphoinositide sensors in HEK293 cells (Borbiro et al., 2015). The difference between the two stimuli were less pronounced than in DRG neurons; capsaicin and carbachol evoked comparable decreases in $PI(4,5)P_2$ even though the effect of capsaicin was faster and somewhat more complete. Carbachol on the other hand induced a much smaller decrease in PI(4)P levels than capsaicin (Borbiro et al., 2015). It is not clear why Ca^{2+}-induced PLCδ activation is more efficient than PLCβ activation in reducing PI(4)P levels, as most PLC isoforms prefer $PI(4,5)P_2$ over PI(4)P, some possible scenarios are discussed in (Lukacs et al., 2013b).

Phosphoinositides, especially $PI(4,5)P_2$ are required for the activity of many different ion channels (Suh and Hille, 2008; Logothetis et al., 2015). Thus the robust depletion of phosphoinositides induced by TRPV1 activation is likely to influence the activity of other ion channels. Accordingly, capsaicin has been shown to inhibit several different ion channels in DRG neurons, and for inhibition of KCNQ channels (Zhang et al., 2011) and for inhibition of TRPA1 (Akopian et al., 2007) inclusion of $PI(4,5)P_2$ in the whole cell patch pipette alleviated capsaicin-induced inhibition. For inhibition of Voltage-gated Ca^{2+} channels (Wu et al., 2006), P2X channels (Stanchev et al., 2009), HCN channels (Kwak, 2012) and for voltage gated Na^{+} channels (Liu et al., 2001), the role of phosphoinositides has not been tested, see details at the discussion of the individual channels. Local capsaicin evokes intense burning pain, but paradoxically, it is also used as a local analgesic, because of the desensitization of the nociceptor neurons, which includes many processes, including desensitization of the channel itself, and potentially inhibition of some of the other ion channels described here (Szallasi and Blumberg, 1999).

5. Downstream signaling – Protein Kinase C (PKC)

PKC enzymes are classical serine threonine kinases with 10 family members in mammals (Newton, 2010). Most of them are activated downstream of PLC by DAG and conventional isoforms are also stimulated by Ca^{2+}. Various PKC isoforms have been shown to be involved in pain sensitization (Velazquez et al., 2007). PKCε received the most attention; it has been shown

to be involved in thermal hyperalgesia mediated by bradykinin-induced sensitization of the heat and capsaicin sensitive TRPV1 channels (Cesare et al., 1999). PKCε deficient mice have reduced thermal and mechanical hyperalgesia induced by epinephrine, and a PKCε selective inhibitory peptide reduced both enhancement of TTX resistant Na^+ currents and carrageenan-induced hyperalgesia in rats (Khasar et al., 1999). Other PKC isoforms may also play roles in pain sensitization in a modality specific manner. Deletion of PKCβ, PKCγ or PKCδ, but not PKCα, attenuated thermal hyperalgesia induced by complete Freund's adjuvant (CFA) injection (Zhao et al., 2011). Mechanical allodynia induced by CFA, or nociceptive behaviors induced by formalin, on the other hand were not affected by deletion of PKCβ, PKCγ or PKCδ, or PKCα (Zhao et al., 2011), pointing to the potential modality dependent involvement of various PKC isoforms in sensitization of DRG neurons.

6. Ion channels primarily activated by PLC signaling

Activation of PLC does not only lead to Ca^{2+} release from intracellular stores and activation of PKC. Downstream signaling pathways also activate ion channels in the plasma membrane. We briefly discuss three groups of such channels below.

6.1. Store-operated orai1 channels

Orai1 channels are Ca^{2+}-selective ion channels activated by the IP_3-induced depletion of the Ca^{2+} stores in the endoplasmic reticulum (ER) that occurs during PLC activation (Putney, 2007). Loss-of-function mutations of orai1 cause sever immunodeficiency in humans by interfering with lymphocyte function (Feske et al., 2006). Orai1 is activated by the ER membrane resident STIM1 protein that clusters in response to Ca^{2+} depletion and activates orai1 by direct interaction via its CAD domain (Park et al., 2009). Both orai1 and STIM1 are expressed in DRG neurons and store operated Ca^{2+} currents could be detected in these cells (Gemes et al., 2011). Furthermore store operated Ca^{2+} entry was increased in an axonal injury model (Gemes et al., 2011). These measurements were performed in isolated cell bodies of DRG neurons, where the ER is clearly present. It has also been shown that the nerve terminals of free nerve endings in the skin contain axonal reticulum, the equivalent of the ER, making it possible that store operated Ca^{2+} channels function not only in the cell bodies, but also at the nerve terminals (Kruger et al., 2003). Interestingly, heat over 35C° has been shown to induce clustering of STIM1 and activation of store operated Ca^{2+} entry (Xiao et al., 2011). While the role of store operated orai1 channels in peripheral sensory functions is far from being elucidated, it was shown that a store-operated channel blocker had significant analgesic effects; but this may have been due to inhibiting orai1 channels in the dorsal horn of the spinal cord (Xia et al., 2014).

Store operated Ca^{2+} entry and orai1 function is positively influenced by phosphoinositides in various ways. The poly-basic region of STIM1 may interact with phosphoinositides and it was shown that even though phosphoinositides are not essential for, they contribute to STIM1 accumulation at ER–PM junctions (Walsh et al., 2010). Another study found that depletion of both $PI(4,5)P_2$ and PI(4)P using PI4K inhibitors, but not selective depletion of $PI(4,5)P_2$ using an inducible 5-phosphatase, inhibited store operated Ca^{2+} entry (Korzeniowski et al., 2009). This topic was reviewed recently in more detail (Cao et al., 2015).

6.2. TRPC-channels

All TRPC channels are activated downstream of PLC (Putney, 2004). TRPC3, TRPC6 and TRPC7 are directly activated by DAG, an effect independent of PKC, but the activation mechanism of the rest of the family has not been fully elucidated despite almost 20 years of intensive research (Putney and Tomita, 2011; Rohacs, 2013). TRPC channels are ubiquitously expressed, with most cell types having multiple isoforms. DRG neurons are not exception, several TRPC family members are present in them, with TRPC3 RNA expressing at especially high levels (Gerhold et al., 2013; Vandewauw et al., 2013; Thakur et al., 2014). Accordingly, application of oleylacylglycerol (OAG), a DAG analogue induces clear Ca^{2+} signals in DRG neurons (Kress et al., 2008). TRPC3 has been proposed to mediate Ca^{2+} signals and ionic currents evoked by IgG immune complexes in rat DRG neurons (Qu et al., 2012). Also, knockdown of TRPC3 has been shown to inhibit Ca^{2+} signals evoked by UTP or activation of proteinase activated receptors (Alkhani et al., 2014). While the role of PLC-activated TRPC currents in DRG neurons has not been elucidated yet, it was shown that nerve injury upregulated TRPC4 in rat DRG-s (Wu et al., 2008). Interestingly, another article reported downregulation of TRPC3, 4 and 5 in a nerve injury model in rats (Staaf et al., 2009). Nerve growth factor has been shown to regulate expression level of TRPC3 (Luo et al., 2007). TRPC3 and TRPC6 are also good candidates to be activated by Mrgpr receptors; it was shown for example that in TRPA1 negative DRG neurons, chloroquine-induced Ca^{2+} signals were inhibited by antagonists of TRPC channels (Than et al., 2013).

Two additional functions for TRPC channels have been proposed in DRG neurons, which are independent of PLC-mediated activation. Various TRPC channels have been shown to be mechanically activated, but at least for TRPC1 and for TRPC6 this notion is debated (Gottlieb et al., 2008). TRPC1 was proposed to be a stretch activated ion channel (Maroto et al., 2005), and also to play a role in light touch sensation (Garrison et al., 2012). TRPC6 was also proposed to be activated by membrane stretch (Spassova et al., 2006). Combined deletion of TRPC3 and TRPC6 caused deficits in light touch (Quick et al., 2012), these deficits however were quite modest, especially compared to the essentially complete loss of light touch sensation caused by deletion of piezo2 channels in DRG neurons and skin cells (Ranade et al., 2014).

TRPC5 is expressed in DRG neurons, and was shown to be cold sensitive, and proposed to play a role in sensing noxious cold temperatures (Zimmermann et al., 2011). $TRPC5^{-/-}$ mice however did not show significant behavioral deficits in

response to cold, presumably because of compensation by other cold sensitive ion channels (Zimmermann et al., 2011). Most other studies however found very low RNA levels for TRPC5 compared TRPC3 in DRG neurons (Gerhold et al., 2013; Vandewauw et al., 2013; Thakur et al., 2014).

Phosphoinositides regulate TRPC channels in a complex fashion, discussion of which is beyond the scope of this review. Briefly, the emerging picture is that TRPC channels, just like most other TRP channels, require $PI(4,5)P_2$ for optimal functioning, and substantial depletion of this lipid limits their activity (Imai et al., 2012; Itsuki et al., 2014). $PI(4,5)P_2$ may also exert an additional negative effect on some TRPC channels, see for example (Trebak et al., 2009), relief from which during PLC activation could potentially contributing to their activation. This topic has been recently reviewed in more detail (Rohacs, 2014).

6.3. Calcium-activated chloride channels (Cl_{Ca})

Cl_{Ca} channels are encoded by members of the TMEM16 family; the first member that was characterized is TMEM16A (Schroeder et al., 2008), also called Anoctamin1 or Ano1 (Yang et al., 2008). Cl^- channels are usually inhibitory, but in DRG neurons they are excitatory, because the reversal potential of Cl^- is more positive than the resting membrane potential, due to its relatively high intracellular concentration (Liu et al., 2010). Ano1 is expressed in DRG neurons, and it was shown that bradykinin exerts its excitatory effect on DRG neurons via activating Ano1 and inhibiting voltage gated KCNQ K^+ channels (Liu et al., 2010). It was also shown that Ano1 is selectively activated by Ca^{2+} signals evoked by GPCR stimulation compared to Ca^{2+} influx via voltage gated Ca^{2+} channels, because of the colocalization of the receptors with Ano1 (Jin et al., 2013). Ca^{2+} influx via TRPV1 also activates Ano1, contributing to the depolarization induced by capsaicin (Takayama et al., 2015). Ano1 was reported to be inhibited by $PI(4,5)P_2$ (Pritchard et al., 2014), an effect that may potentially contribute to its activation by bradykinin, or capsaicin. Another article however found no effect of various interventions that affect phosphoinositide metabolism on Ano1 activity (Tian et al., 2013). Ano1 was also proposed to be a noxious heat sensor (Cho et al., 2012).

7. PI3K signaling in DRG neurons

DRG neurons also express Receptor Tyrosine Kinases, such as the Nerve Growth Factor (NGF) receptor. NGF exerts trophic effects on neonatal and fetal DRG neurons and plays important roles in their development. NGF also exerts acute pro-inflammatory effects, for example it was shown to sensitize TRPV1 channels, which was proposed to proceed via activating PLC and the depletion of $PI(4,5)P_2$ (Chuang et al., 2001). Later however several papers concluded that acute potentiation by NGF proceeds via increased trafficking of the TRPV1 protein in a PI3K sensitive manner (Bonnington and McNaughton, 2003; Zhang et al., 2005; Stein et al., 2006).

8. Ion channels in sensory neurons

Sensory neurons respond to mechanical, chemical or thermal stimuli. The primary output of the peripheral processes of DRG neurons is generation of action potentials that will eventually trigger the release of glutamate in the central terminals to stimulate secondary neurons in the dorsal horn of the spinal cord. Ion channels that generate these electrical signals in primary sensory neurons can be roughly divided into two categories: sensory and non-sensory ion channels. Non-sensory ion channels that set the resting membrane potential, generate the action potential and initiate transmitter release, such as background K^+ channels, voltage gated Na^+, K^+ and Ca^{2+} channels, are not specific to DRG neurons. Sensory ion channels that respond to thermal, chemical or mechanical cues and initiate action potentials by depolarizing the cell membrane are often specifically expressed in sensory neurons. Many sensory ion channels belong to the Transient Receptor Potential (TRP) family (Clapham, 2003), but not all sensory channels are TRPs, and not all TRPs are sensory (Wu et al., 2010). Sensory channels are often multimodal, and can be activated by multiple stimuli. This division, while useful didactically, is somewhat arbitrary, as some non-sensory ion channels can also be modulated by temperature or mechanical forces (Maingret et al., 2000; Hao et al., 2013).

9. Sensory TRP channels

The regulation of TRP channels by the PLC pathway (Rohacs, 2013), by phosphoinositides (Rohacs, 2014) and by GPCR-s in general (Veldhuis et al., 2015) have been recently reviewed. Here we briefly describe the TRP and other sensory channels found in DRG and TG neurons and discuss their regulation by the phosphoinositide signaling pathway.

9.1. TRPV1

TRPV1 is a heat- and capsaicin-activated ion channel; it is probably the most intensively studied sensory ion channel (Bevan et al., 2014). Its role as a physiological heat sensor is somewhat debated (Dhaka et al., 2006), but it is very well established to be important for thermal hyperalgesia (Vriens et al., 2014b). Thermal hyperalgesia is mediated by sensitization of TRPV1 by inflammatory mediators, such as bradykinin or prostaglandins. Sensitization refers to the shift in the activation

curve of the channel to heat, capsaicin and low extracellular pH, that makes it easier for these stimuli to open the channel. The role of PKC in acute sensitization of TRPV1 is very well established (Numazaki et al., 2002; Bhave et al., 2003; Lukacs et al., 2013b). Depletion of $PI(4,5)P_2$ and relief from inhibition by this lipid has also been proposed to play a role in acute sensitization (Chuang et al., 2001; Cao et al., 2013), but this effect is probably auxiliary to PKC (Lukacs et al., 2013b), and somewhat controversial. As we have recently reviewed this topic in detail (Rohacs, 2015), its detailed discussion is beyond the scope of this review.

The activity of TRPV1 similar to most other TRP channels depend on the presence of phosphoinositides (Stein et al., 2006; Lukacs et al., 2007, 2013a; Klein et al., 2008; Poblete et al., 2014), mainly $PI(4,5)P_2$, with a potential contribution of PI(4)P in a cellular context (Rohacs, 2014). These channels undergo desensitization during prolonged exposure to capsaicin. Several different Ca^{2+} dependent mechanisms, such as calmodulin (Numazaki et al., 2003; Rosenbaum et al., 2004; Lishko et al., 2007) and calcineurin (Docherty et al., 1996; Mohapatra and Nau, 2005) have been proposed to play a role in desensitization, but depletion of $PI(4,5)P_2$ and PI(4)P by Ca^{2+}-induced PLC activation is emerging as a key mechanism (Liu et al., 2005; Lishko et al., 2007; Lukacs et al., 2007, 2013b) reviewed in (Rohacs, 2015).

9.2. TRPV2

TRPV2 was originally described as a noxious heat sensor (Caterina et al., 1999). TRPV2 RNA is expressed in DRG neurons at high levels (comparable to that of TRPV1) (Gerhold et al., 2013; Vandewauw et al., 2013; Thakur et al., 2014), and TRPV2 protein was also detected in medium and larger DRG neurons (Caterina et al., 1999). Interestingly, mice lacking this channel have normal thermosensation (Park et al., 2011), but they are more susceptible to perinatal death, and have impaired macrophage phagocytosis (Link et al., 2010). TRPV2 activity depends on $PI(4,5)P_2$ and its depletion has been proposed to play a role in desensitization to its chemical agonist 2-APB in an expression system (Mercado et al., 2010). It was recently proposed that TRPV2 is an intracellular ion channel, upregulated by NGF, playing a role in neurite outgrowth (Cohen et al., 2015).

9.3. TRPV3

TRPV3 was identified as a sensor of moderately warm temperatures in keratinocytes (Peier et al., 2002b; Xu et al., 2002). This channel is often considered a thermo-TRP, but it is essentially not expressed in DRG neurons (Gerhold et al., 2013; Vandewauw et al., 2013; Thakur et al., 2014; Vriens et al., 2014b). While initial reports suggested the involvement of this channel in behavioral responses to warm temperatures, this effect is highly dependent on genetic background and sex (Vriens et al., 2014b). The most likely physiological role of TRPV3 is to regulate skin and hair development (Nilius et al., 2014). Consistent with this idea, mice lacking TRPV3 has altered skin barrier formation and curly hair (Cheng et al., 2010), whereas humans with a gain of function mutation of TRPV3 develop Olmsted syndrome that is characterized by skin and hair abnormalities, palmoplantar and periorificial keratoderma, alopecia and severe itching (Lin et al., 2012). TRPV3 was shown to be negatively regulated by $PI(4,5)P_2$ (Doerner et al., 2011).

9.4. TRPV4

TRPV4 is a mechanically activated ion channel playing important roles in osmosensation (Liedtke and Friedman, 2003). As opposed to the fast and presumably direct activation of piezo channels by membrane stretch, TRPV4 activation by osmotic swelling is slow, and was proposed to proceed via a lipid mediators generated by phospholipase A2 and cytochrome P450 epoxygenase (Vriens et al., 2004). This channel is also activated by heat via a mechanism distinct from that induced by swelling (Vriens et al., 2004). TRPV4 was proposed to be regulated by $PI(4,5)P_2$ both positively (Garcia-Elias et al., 2013) and negatively (Takahashi et al., 2014). Mutations in TRPV4 cause human disease with a puzzling variety of manifestations including skeletal dysplasias and degeneration of motor neurons (Nilius and Voets, 2013). TRPV4 is also activated by moderate heat, but it probably does not play a significant role in thermosensation (Vriens et al., 2014b). TRPV4 is expressed in adult mouse DRG neurons at very low levels compared to other sensory TRP channels (Thakur et al., 2014; Vriens et al., 2014b).

9.5. TRPM3

TRPM3 is a heat activated ion channel expressed in DRG neurons where it was proposed to play a role as a noxious heat sensor (Vriens et al., 2011). Like most thermo TRP channels, TRPM3 also has chemical activators, the most often used one being pregnenolone sulfate (Wagner et al., 2008). Clotrimazole, when co-applied with pregnenolone sulfate, opens an alternative permeation pathway with different pore properties (Vriens et al., 2014a). TRPM3 channel activity induced by pregnenolone sulfate in heterologous expression systems was shown to require the presence of $PI(4,5)P_2$ (Badheka et al., 2015; Toth et al., 2015). Understanding the regulation of TRPM3 by phosphoinositide signaling in DRG neurons will require further studies.

9.6. TRPM8

TRPM8 is a cold- and menthol-activated ion channel expressed in DRG and TG neurons (McKemy et al., 2002; Peier et al., 2002a). Genetic deletion of this channel in mice clearly and unambiguously altered sensitivity to moderately cold temperatures (Bautista et al., 2007; Colburn et al., 2007; Dhaka et al., 2007). TRPM8 was shown to require $PI(4,5)P_2$ for activity both in cellular systems (Liu and Qin, 2005; Rohacs et al., 2005; Varnai et al., 2006; Daniels et al., 2009), and in planar lipid bilayers (Zakharian et al., 2009, 2010; El-Arabi et al., 2012), demonstrating that the lipid is a direct activator of these channels. In the presence of extracellular Ca^{2+}, TRPM8 activity decreases during continuous stimulation by menthol or cold (McKemy et al., 2002), a phenomenon termed desensitization or adaptation. Ca^{2+}-induced activation of PLC has been shown to play an important role in this phenomenon (Rohacs et al., 2005; Daniels et al., 2009; Yudin et al., 2011). The most abundantly expressed Ca^{2+} sensitive PLC isoform in DRG neurons is PLCδ4 (Lukacs et al., 2013b), and we recently found that small TRPM8 positive DRG neurons in PLCδ4$^{-/-}$ mice show larger cold- and menthol-induced currents and the animals were more sensitive to evaporative cold (Yudin and Rohacs, 2015), showing the importance of PLCδ4 in the regulation of TRPM8 *in vivo*.

9.7. TRPA1

TRPA1 was originally described as a noxious cold sensor (Story et al., 2003), but its regulation by cold is controversial (Jordt et al., 2004; Bautista et al., 2006; Kwan et al., 2006; Karashima et al., 2009), and may be species dependent (Chen et al., 2013), see recent reviews on TRPA1 for more details (Vriens et al., 2014b; Zygmunt and Hogestatt, 2014). TRPA1 is a well established noxious chemical sensor, activated by mustard oil, acrolein, formaldehyde and many other compounds mainly by covalent modification (Jordt et al., 2004; Macpherson et al., 2007). This channel plays important roles not only in DRG neurons, but also in sensory nerves innervating the airways, playing important roles in detecting irritants (Bessac et al., 2008). As mentioned earlier, TRPA1 is also involved in chloroquine-induced itch, via activation by G_q-coupled MrgprA3 receptors (Wilson et al., 2011).

Phosphoinositides were also proposed to regulate this channel, but the picture in this regard is as confusing as with cold activation, reviewed in (Rohacs, 2014). Both activating (Karashima et al., 2008) and inhibitory effects (Kim et al., 2008) of $PI(4,5)P_2$ were proposed, but the channel was not inhibited by a rapamycin-inducible 5-phosphatase (Wang et al., 2008), and the purified reconstituted channel was active without $PI(4,5)P_2$ or other negatively charged lipids in planar lipid bilayers raising doubts about its phosphoinositide dependence (Moparthi et al., 2014). Activation of TRPV1 by capsaicin on the other hand inhibited TRPA1, and inclusion of $PI(4,5)P_2$ in the patch pipette alleviated this effect, suggesting dependence on $PI(4,5)P_2$ (Akopian et al., 2007). Bradykinin was shown to potentiate TRPA1 activity (Bandell et al., 2004).

10. Ligand activated and chemosensitive ion channels

Most thermo TRP channels discussed in the previous chapter have chemical activators, and TRPA1 clearly functions as a noxious chemical sensor. Below we will briefly discuss two additional groups of ion channels that are present in DRG neurons, and are regulated by the chemical composition of the extracellular fluid.

10.1. P2X-ATP receptors

Extracellular ATP is an important signaling molecule, playing roles in many cellular processes. ATP acts on either G-protein coupled P2Y receptors, or directly activates P2X non-selective cation channels, which we briefly discuss here. The dominant P2X isoform expressed in DRG neurons is P2X3, with substantial expression of P2X2 and P2X4 (Thakur et al., 2014).

ATP can be released from cells via plasma membrane transport proteins such as pannexins or CALHM channels (Taruno et al., 2013). Keratinocytes for example may release ATP via connexin hemichannels (Barr et al., 2013), and heat activation of TRPV3 in keratinocytes was proposed to transmit information via ATP release (Mandadi et al., 2009), a notion consistent with reduced non-noxious warmth sensitivity of P2X3$^{-/-}$ mice (Souslova et al., 2000). ATP can also be released from damaged cells in a non-specific manner, and P2X3$^{-/-}$ mice showed reduced responses to formalin-induced pain. Responses to noxious thermal and mechanical stimuli however were normal in P2X3$^{-/-}$, but the animals also showed reduced inflammatory hyperalgesia (Souslova et al., 2000).

Several P2X isoforms were shown to require $PI(4,5)P_2$ and to be inhibited by depletion of $PI(4,5)P_2$ (Fujiwara and Kubo, 2006; Bernier et al., 2008a, 2008b); this topic was reviewed recently (Bernier et al., 2013). It was shown that in rat DRG neurons activation of the Gq-coupled P2Y2 receptors inhibit P2X3 via $PI(4,5)P_2$ depletion (Mo et al., 2013). Capsaicin also inhibits P2X3 in TRPV1 expressing cells (Stanchev et al., 2009), and in rat DRG neurons (Piper and Docherty, 2000) but the involvement of phosphoinositides were not examined.

10.2. Acid sensing ion channels (ASIC)

ASIC channels are distant relatives of the Epithelial Na^+ channels (ENaC). They are activated by extracellular acidification and they are expressed in DRG neurons, but their role in sensory functions is controversial (Wemmie et al., 2013). Despite the

well documented regulation of the related ENaC family by phosphoinositides (Pochynyuk et al., 2008), there is no report on phosphoinositide regulation of ASIC channels.

11. Mechanosensitve ion channels

DRG neurons have been shown to display mechanically activated (MA) currents with various inactivation/adaptation kinetics (Hu and Lewin, 2006; Hao and Delmas, 2010; Rugiero et al., 2010). The molecular identity of these ion channels has been a mystery until relatively recently (Sachs, 2010). TRPA1, TRPV4 and ASICS have been proposed earlier to play roles, but the data were controversial (Arnadottir and Chalfie, 2010; Sachs, 2010). The recently identified Piezo2 ion channels are the well-accepted molecular counterparts of the Rapidly Adapting MA current in DRG neurons (Coste et al., 2010), but the proteins that mediate Slowly and Intermediate Adapting MA current have not yet been identified.

11.1. Piezo2

Piezo 2 and its close relative Piezo1 are bona fide mechanosensitive ion channels that generate large mechanically-induced ionic currents when expressed in heterologous systems (Volkers et al., 2014). Genetic deletion of Piezo2 in DRG neurons and in Merkel cell results in a profound loss of gentle touch sensation in mice (Ranade et al., 2014). Piezo2 currents have been shown to be potentiated by activation of bradykinin receptors with the involvement of PKC (Dubin et al., 2012). Rapidly adapting MA current in DRG neurons were also shown to be potentiated by activation of P2Y receptors by extracellular UTP and ATP (Lechner and Lewin, 2009). Activation of TRPV1 by capsaicin on the other hand resulted in a profound inhibition of Piezo2 currents in DRG neurons expressing both TRPV1 and Piezo2. This inhibition was reproduced both in heterologously expressed Piezo1 and Piezo2, and the effect was alleviated by the inclusion of either $PI(4,5)P_2$ or PI(4)P in the patch pipette (Borbiro et al., 2015).

12. Ion channels involved in setting the resting membrane potential, generation of action potentials and transmitter release

12.1. Two-pore (2P) K^+ channels

2P K^+ channels are also called background K^+ channels, because they are constitutively open, thus they are important determinants of the resting membrane potential (Enyedi and Czirjak, 2010). These channels are also regulated by a large number of factors, including temperature (Maingret et al., 2000), mechanical forces (Honore et al., 2006) and various signaling pathways (Enyedi and Czirjak, 2010). Changes in the activity of 2P channels can affect the resting membrane potential, leading to increased, or decreased excitability. Several 2P channels are expressed in sensory neurons (Thakur et al., 2014) and 2P channels have been shown to significantly contribute to the resting membrane potential in these cells (Du et al., 2014). Genetic deletion of TREK-1 (KCNK2) resulted in enhanced sensitivity to mechanical stimuli and painful heat (Alloui et al., 2006). TREK-1 is positively modulated by heat, and closure of a background channel upon cooling was proposed to play a role in cold transduction (Viana et al., 2002), but TREK-$1^{-/-}$ mice showed normal cold sensitivity (Alloui et al., 2006). TRESK (KCNK18) (Czirjak et al., 2004) is also expressed in DRG neurons (Dobler et al., 2007), and its inhibition by hydroxy-alpha-sanshool was proposed to be responsible for the tingling pungency of Szechuan peppers (Bautista et al., 2008). Interestingly, functional knockout of TRESK channels in mice resulted in no change in resting membrane potential in DRG neurons, but it increased cellular excitability (Dobler et al., 2007). It was shown that in peripheral axotomy, TRESK channels are downregulated, and this contributes to increased excitability (Tulleuda et al., 2011).

TASK, TREK-1 and TRAAK channels were proposed to be regulated by $PI(4,5)P_2$ (Chemin et al., 2005; Lopes et al., 2005), but their inhibition by PLC coupled agonists have been shown be mediated by direct binding of G_q subunits, rather than $PI(4,5)P_2$ depletion (Chen et al., 2006). More recently, it was proposed that PLC-coupled agonists inhibit TASK channel via DAG (Wilke et al., 2014). We are not aware of any data on regulation of 2P channels in DRG neurons by phosphoinositide signaling.

12.2. Voltage gated K^+ channels

Voltage gated K^+ (Kv) channels are the most diverse superfamily of ion channels (Yu and Catterall, 2004) and DRG neurons express many different Kv-s (Du and Gamper, 2013; Thakur et al., 2014). Here I will focus on regulation of the KCNQ (Kv7.x) channels that mediate M-currents, which are very well established to depend on $PI(4,5)P_2$ and to be regulated by changes in phosphoinositide levels (Suh and Hille, 2002; Zhang et al., 2003). KCNQ channels are low voltage activated, and contribute to setting the resting membrane potential in DRG neurons (Du et al., 2014), thus their inhibition has a significant effect on cellular excitability.

KCNQ2 (Kv7.2) is the major KCNQ transcript in DRG neurons, it is mainly expressed in small diameter neurons, and its expression level was shown to decrease upon nerve injury contributing to increased excitability in neuropathic pain (Rose et al., 2011). Activation of proteinase-activated PAR-2 receptors was shown to decrease KCNQ mediated M-currents in DRG neurons, and this inhibition required both the depletion of $PI(4,5)P_2$ and the increase in cytoplasmic Ca^{2+} (Linley et al., 2008). Bradykinin was also shown to inhibit M-currents in DRG neurons (Liu et al., 2010). As mentioned earlier, chloroquine also

inhibits KCNQ channels via the activation of MrgprA3 receptors in a PLC dependent manner (Crozier et al., 2007). Finally, activation of TRPV1 by capsaicin was shown to inhibit KCNQ channels via $PI(4,5)P_2$ depletion (Zhang et al., 2011).

12.3. Voltage gated Na^+ (VDNaC) channels

VDNaC channels generate the upstroke of action potentials; they are targets for local anesthetics such as lidocaine, and mutations in some of them cause syndromes with inability to sense pain (Waxman and Zamponi, 2014). There is no data currently on phosphoinositide sensitivity of VDNaC channels, and very little is known on their regulation by this pathway. Capsaicin was shown to inhibit VDNaC in TG neurons, and the extent of inhibition was proportional to the inward current evoked by capsaicin, but the role of phosphoinositide signaling was not examined (Liu et al., 2001). Stimulation of NK-1 receptors was reported to enhance the activity of tetrodotoxin-resistant Nav1.8 channel is small diameter DRG neurons, in a manner dependent on PKCε, an effect that may contribute to inflammatory hyperalgesia (Cang et al., 2009).

12.4. Voltage gated Ca^{2+} channels (VGCC)

The classical characterization of VGCC to T, N and L-type is based on work in DRG neurons (Nowycky et al., 1985). Unbiased high throughput RNA sequencing show high levels of expression of Cav2.2 (N-type), Cav1.2 (L-type), Cav3.2 and 3.3 (T-type) in DRG neurons (Thakur et al., 2014). N-type VGCC has been shown by multiple approaches to require $PI(4,5)P_2$ for activity (Wu et al., 2002; Gamper et al., 2004; Suh et al., 2010), reviewed in (Gamper and Rohacs, 2012). Cav1.2 and Cav1.3 L-type channels were also reported to be partially inhibited by $PI(4,5)P_2$ depletion, but T-type channels were not affected (Suh et al., 2010).

N-type VGCC are well known to be rapidly inhibited by G_i-coupled GPCR-s via $G\beta\gamma$ subunits. Activation of G_q coupled receptors, however, also exerts a slower inhibition on these channels via $PI(4,5)P_2$ depletion in superior cervical ganglion cells (Gamper et al., 2004). N-type VGCC in DRG neurons have been reported to be inhibited by two different G_q coupled receptors: MrgprC (Li et al., 2014) and purinergic P2Y receptors (Gerevich et al., 2004). The role of phosphoinositide depletion however was not examined in either of these cases. There are several reports showing that capsaicin inhibits VGCC in TRPV1 positive DRG neurons (Bleakman et al., 1990; Hagenacker et al., 2005; Wu et al., 2005, 2006; Docherty et al., 1991; Comunanza et al., 2011), but the role of phosphoinositide signaling was not examined in any of these papers. Given the clear dependence of N-type channels on $PI(4,5)P_2$ and the robust depletion of $PI(4,5)P_2$ induced by TRPV1 activation (Lukacs et al., 2013b) this mechanism is feasible, at least for inhibition of N-type channels.

12.5. Hyperpolarization-activated cyclic Nucleotide-gate (HCN) channels

HCN channels are found in neurons and other excitable tissues that fire action potentials rhythmically. HCN1 and HCN2 channels are expressed in DRG neurons (Acosta et al., 2012), HCN2 was shown to play a role in mechanical, but not heat hyperalgesia in chronic inflammation (Schnorr et al., 2014), and HCN2 levels were increased after axotomy (Smith et al., 2015). Capsaicin was shown to inhibit HCN channels in TRPV1 positive DRG neurons in a Ca^{2+} dependent manner (Kwak, 2012); the role of phosphoinositides were not addressed, but the effect was inhibited by cyclosporine, implying the role of calcineurin. HCN channels were proposed to be positively regulated by $PI(4,5)P_2$ by shifting the activation of the channel to more depolarized voltages (Zolles et al., 2006). In another publication, however, activation of PLC coupled receptors resulted in a shift of activation gating to more negative voltages, the opposite of what was expected if phosphoinositides positively regulate HCN channels (Pian et al., 2007).

13. Conclusions

This review attempted to discuss signaling through phosphoinositides in peripheral sensory neurons, with focus on effects on ion channels. I tried to be comprehensive, yet brief, a combination inevitably leading to some oversimplification. The role of PLC signaling in acute inflammatory sensitization has been very well established, and the role of this signaling pathway in certain forms of itch is emerging. The diversity of sensory neurons and the pleiotropic nature of phosphoinositide signaling make the picture complex however. There is an abundance of information available on this topic, but a lot of dots need to be connected by future research to have a clearer picture on the details in many cases.

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