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Channelopathies linked to plasma membrane phosphoinositides

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Abstract

The plasma membrane phosphoinositide phosphatidylinositol 4,5-bisphosphate (PIP_2) controls the activity of most ion channels tested thus far through direct electrostatic interactions. Mutations in channel proteins that change their apparent affinity to PIP_2 can lead to channelopathies. Given the fundamental role that membrane phosphoinositides play in regulating channel activity, it is surprising that only a small number of channelopathies have been linked to phosphoinositides. This review proposes that for channels whose activity is PIP_2-dependent and for which mutations can lead to channelopathies, the possibility that the mutations alter channel-PIP_2 interactions ought to be tested. Similarly, diseases that are linked to disorders of the phosphoinositide pathway result in altered PIP_2 levels. In such cases, it is proposed that the possibility for a concomitant dysregulation of channel activity also ought to be tested. The ever-growing list of ion channels whose activity depends on interactions with PIP_2 promises to provide a mechanism by which defects on either the channel protein or the phosphoinositide levels can lead to disease.

Keywords

PIP_2; Phosphoinositides; Channelopathies; Ion Channels; Channel-PIP_2 interactions; Channel activity; Modulation of channel activity

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Introduction

Phosphatidylinositol 4,5-bisphosphate (PtdIns(4,5)P_2 or PIP_2) is the most abundant phosphoinositide localized at plasma membranes of eukaryotic cells. It is a well-recognized lipid precursor molecule that has for more than three decades garnered appreciation as a regulator of many physiological processes. Since the mid-1990s, when three reports of PIP_2 regulation of K_{ATP} channel activity appeared [53, 60, 78], there has been an explosion of reports demonstrating a dependence of the activity of most ion channels on the presence of phosphoinositides. Numerous reviews have appeared discussing in detail the activity dependence of specific ion channel types. General reviews also appear annually highlighting general principles that may apply across different channel types (e.g., [63, 83, 195]). Yet, as our appreciation grows regarding the central role these signaling phospholipids play in regulating channel activity, one wonders why the number of ion channel diseases described to be linked to phosphoinositide defects are relatively sparse. Here, we first review diseases known to be caused by dysregulation of phosphoinositide levels and ask how expected concomitant effects on ion channel activity might contribute to the disease phenotype. Next, we update the ever-growing list of ion channels, whose activity is reported to depend on phosphoinositides, and summarize key features of their physiology and pathophysiology. We then review ion channel channelopathies that have been directly linked to altered interactions with PIP_2. We finally conclude by asking whether, given the central role of phosphoinositide control of ion channel activity, we ought to be clarifying whether mechanisms of disease for phosphoinositide-dependent channels operate by affecting phosphoinositide regulation of their activity.

PIP_2 and disease

Aberrant regulation of PIP_2 gives rise to a plethora of diverse diseases, as might be expected for a ubiquitous signaling phospholipid with central importance in such diverse functions as neuronal signaling, regulation of apoptosis, and actin remodeling. Many diseases currently attributed to aberrant PIP_2 regulation are linked to disorders of the phosphoinositide pathway, which is briefly reviewed below.

The precursor phosphatidylinositol (PtdIns) is subject to reversible phosphorylation at the 3, 4, and 5-hydroxyl positions of the inositol ring, potentially giving rise to seven different phosphoinositide molecules. Due to tight temporal and spatial restriction of the kinases and phosphatases governing phosphoinositide generation, different phosphoinositides are largely confined to different membranous compartments, with PIP_2 concentrated at the plasma membrane. Indeed, PIP_2 interaction with integral membrane proteins appears to play a major functional role, with PIP_2 substrates including enzymes with the pleckstrin homology domain, scaffolding proteins, and ion channels, the subject of this review. The seminal importance of PIP_2 in regulated secretion pathways has been demonstrated in neuroendocrine cells, including the ability of PIP_2 to direct and accelerate targeting of synaptotagmins involved in vesicle fusion. PIP_2, generated by 5-phosphokinases from PtdIns4 at the plasma membrane, is essential for the early steps of endocytosis, including adaptor protein recruitment and actin molecular motor operation. The endocytic pathway

further requires 5-phosphatase activity and subsequent removal of PIP_2 from endocytic microdomains to complete vesicle fusion and release [208].

Due to PIP_2 involvement in several essential cellular tasks at the plasma membrane, it is not surprising that aberrant PIP_2 generation could give rise to diseases with variable clinical phenotypes. The oculocerebrorenal syndrome of Lowe, characterized by mental retardation, cataracts, and renal Fanconi syndrome, is linked to mutations in the OCRL1 gene, a known inositol 5-phosphatase with a preferred in vitro substrate of PIP_2. How loss of OCRL1 function leads to the severe clinical pathology in Lowe syndrome is unclear but may underscore the importance of tight regulation of phosphoinositide generation. There has been much interest as well in lithium treatment of bipolar disorder and impact on phosphoinositides. Lithium is known to inhibit inositol monophosphatase, leading to reduced pools of myoinositol, a precursor to PtdIns. Whether inositol depletion by lithium accounts for the mood-stabilizing effects in bipolar disease patients remains a controversial issue, especially since new cell signaling targets for lithium have been found, including PKC and GSK3β [69].

There has been a flurry of interest recently in neurode-generative diseases and PIP_2 metabolism, and importantly, the protein aggregates postulated to have a central role in neurodegeneration have direct or indirect impacts on membrane PIP_2. Oligomeric Aβ42 peptide, known to accumulate in the brains of Alzheimer's disease patients, was shown to decrease PIP_2 levels in both acute and chronic treatments of primary cortical neurons in culture without altering the levels of PIP_2 metabolic enzymes, and in a reversible manner. The selective PIP_2 decrease was shown to involve phospholipase C-mediated hydrolysis and calcium, while synaptojanin-1 (an inositol 5-phosphatase) haploinsufficient neurons were protected from the PIP_2 decreasing effect of oligomeric Aβ42, possibly due to their already increased PIP_2 levels [8].

If proper PIP_2 levels are indeed crucial to normal synaptic function, then it is perhaps not surprising that dysregulation can produce cognitive deficits. SYNJ1, coding for synaptojanin-1, is localized to chromosome 21q and is subsequently a potential player in the cognitive deficits of Trisomy 21 or Down's syndrome. A mouse model of Down's syndrome displayed elevated levels of synaptojanin-1, and transgenic overexpression of synaptojanin-1 in normal mice was linked to deficits in behavioral learning. Utilizing the Morris water maze task and limited training, transgenic SYNJ1 mice spent equal amount of time in each maze quadrant, while wild-type mice spent the majority of time in the quadrant containing the hidden platform. Only with extensive training could the transgenic mice reach equivalent scores on the maze with the wild-type mice, indicating a deficit in spatial learning ability linked to phosphoinositide metabolism [210].

Further evidence of the role of PIP_2 in central nervous system (CNS) function comes from its interaction with myelin basic protein (MBP), an essential component in the myelination pathway that may be disrupted in demyelinating diseases like multiple sclerosis. PIP_2 was shown to interact with MBP in both primary oligodendrocytes and an oligodendrocyte precursor cell line, oli-Neu. A mutant form of MBP that does not localize to the plasma membrane is unable to localize to PIP_2-rich regions, and a reduction in PIP_2 levels by

synaptojanin-1 overexpression and wortmannin treatment resulted in less MBP targeted to the plasma membrane. Further disruptions in either PIP_2 charge or localization prevented MBP recruitment to the membrane, implicating PIP_2 as the anionic phospholipid required for proper MBP localization and function [141].

Given its ubiquitous nature, diseases associated with PIP_2 function can have far-reaching multi-organ pathological consequences, as shown in the ciliopathy Joubert syndrome. The central tenet of ciliopathies is that an impairment of cilia function in several cell types results in dysregulated proliferation in response to external cues and subsequent formation of cystic masses in multiple organs. Individuals with Joubert syndrome were found to have associated mutations in the INPP5E gene, an inositol 5-phosphatase, that impaired normal activity on the substrates PIP_3 and PIP_2. Primary fibroblasts isolated from patients with mutant INPP5E had reduced cilia number and length after serum stimulation compared to control fibroblasts. Interestingly, this implicates aberrant regulation of phosphoinositides in impaired function of the cilia [17].

Many of the diseases described thus far have a central theme: either too much or too little PIP_2, resulting from impairment of normal phosphoinositide metabolism. We would predict that dysregulation of PIP_2 levels would result in dysregulation of channel activity in the cells and tissues where it occurs. This prediction points us in the direction of examining for possible electrophysiological phenotypes in such cases of PIP_2 dysregulation.

We will continue next by examining proteins that normally interact with PIP_2 but are not directly involved in its metabolic regulation, namely, PIP_2-sensitive ion channels. Ion channels are involved in a diverse array of biological processes such as in the control of cellular excitability of neurons or neuroendocrine cells and neurotransmitter and insulin release, in cellular excitability of muscle cells of all types and muscle contraction, in sensory modalities, in salt transport across epithelia, and in T-cell activation.

Ion channels and transporters regulated by phosphoinositides

Tables 1 and 2 list ion channels whose activity has been reported to depend on phosphoinositides and their tissue distribution. This list builds on previous efforts by other investigators in the field over the past 5 years (e.g., [63, 194, 195]). The danger of compiling lists of this sort in such a rapidly evolving field is that they are both unlikely to be all inclusive and certain to be outdated even before published. Nonetheless, Tables 1 and 2 do make the point that very different ion channel types, both in terms of structural and functional diversity, utilize PIP_2 to control their activity in the plasma membrane.

Several studies have concluded that channel-PIP_2 interactions control directly channel gating (e.g., for Kir channels [52, 119, 122, 218]). Yet, the details of how channel-PIP_2 interactions lead to channel gating and which gates are affected are awaiting further structural and functional analysis.

Analysis of 25 crystallographic structures of a diverse group of proteins that were solved in complex with phosphoinositides revealed a number of generalizable common features [175], among which were that (a) there was a strong electrostatic component in the protein–

phosphoinositide interaction, involving at least two positively charged residues, and (b) the ability of a specific phosphoinositide to bind a protein depended in its ability to fit into a binding site, and its affinity depended on the number of specific interactions in which it would engage. As three-dimensional structures of ion channel complexes with phosphoinositides become available along with molecular dynamic simulations, they promise to give us insights as to the missing details of the specific channel-PIP_2 interactions and how they lead to channel gating (e.g., [119, 175]).

Below, we give a brief description of the PIP_2-sensitive channels described in the literature thus far and in the order they appear in Tables 1 and 2, with a special emphasis into their key physiological and potential pathophysiological roles, particularly as suggested by transgenic animal models. There exist many comprehensive reviews detailing our current knowledge of these channels. Here, we aim to give our readers an overview of the physiology and pathophysiology that PIP_2-sensitive channels are involved in.

Kir channels

Inwardly rectifying K^+ (Kir) channels pass K^+ ions better in the inward than outward direction, a phenomenon mediated by a physical block of outward current by Mg^{2+} ions and polyamines that bind to the transmembrane and cytoplasmic regions of these channels. They possess two transmembrane domains that form the basic pore-conducting structure in K^+ channels. They are major contributors to the resting membrane potential of cells they are expressed in [76]. All Kir channels depend on the presence of PIP_2 to maintain their activity. Kir channel structures have allowed mapping onto the protein structure of amino acid residues, mutation of which alters channel-PIP_2 interactions [119]. Interestingly, diverse modulators of Kir channel activity, such as the βγ subunits of G proteins, intracellular Na^+, and phosphorylation by different kinases (Kir3) and protons (Kir1.1), depend on phosphoinositides for their effects and act in close proximity to residues implicated in phosphoinositide binding [120]. This has led to the hypothesis that modulators exert their effects by altering channel-PIP_2 interactions.

Kir1 channels (first referred to as ROMK—rat outer medullary K^+—channels) come in six alternatively spliced mRNA isoforms that give rise to three distinct proteins (Kir1.1–1.3) with differing lengths in their NH_2 terminus. They show weak rectification and are blocked by internal acidification. Kir1.1 is localized at the apical surface of kidney epithelial cells and physiological as well as transgenic work supports its function in renal NaCl absorption. Kir1.1 knockout in mice results in Bartter's syndrome, an autosomal recessive renal tubulopathy characterized by renal salt wasting and metabolic alkalosis, among other phenotypes [76].

Kir2 channels (first referred to as IRK—inwardly rectifying K^+—channels) are constitutively active and exhibit strong inward rectification. There are five Kir2 subfamily members (Kir2.1–2.4 and a recently discovered Kir2.6) that can exist as homomers or heteromers [76, 178]. These channels keep the resting potential close to the K^+ equilibrium potential and contribute to the long-lasting action potential plateau in a number of different cells. Dysfunctions in Kir2.1 caused by mutations reducing its activity result in Andersen's syndrome, an autosomal-dominant disorder, characterized by delayed ventricular

repolarization (manifested as a prolonged QT interval on an electrocardiogram), syncope, and sudden death [209]. Kir2.1 knockout mice reproduce some phenotypes of Andersen's syndrome and show defects in vascular tone. Gain of function mutations in Kir2.1 can lead to short QT syndrome that can lead to sudden cardiac death, syncope, and/or atrial fibrillation [76].

Kir3 channels (first referred to as GIRK—G protein-sensitive inwardly rectifying K^+—channels) are distinguished from other inward rectifiers in that their activity is regulated by G proteins. Kir3.1–Kir3.4 exist as homomers (except Kir3.1) or heteromers. Kir3.2 and Kir3.3 predominate in the nervous system, while Kir3.4 in the atria of the heart. Kir3 currents exhibit strong inwardly rectifying characteristics. ACh released by the vagus nerve activates K_{ACh} (Kir3.1/Kir3.4), slowing the heart rate and shortening the atrial myocyte action potential and effective refractory period. Kir3.1 or Kir3.4 knockout mice lack the typical K_{ACh} currents. Kir3.4 knockout mice exhibit unchanged ambulatory heart rate, reduced heart rate variability, and resistance to atrial fibrillation [76]. Neuronal Kir3 channels modulate synaptic transmission underlying memory storage, control of seizure activity, reinforcement of addictive substance use, and regulation of pain sensation. Consistent with their broad distribution and negative feedback on excitatory synaptic transmission, Kir3.1- and Kir3.2-knockout mice exhibit many behavioral phenotypes including hyperactivity, reduced anxiety behavior, diminished administration of addictive substances, lower seizure threshold, hyperalgesia, and diminished opioid induced analgesia [133, 134, 163].

Kir4 and Kir5 channels can form heteromers with each other. Kir5.1, like Kir3.1, is not functional as a homomer but confers distinct phenotypes to heteromers with Kir4 subunits (e.g., intracellular pH and Na^+ sensitivity). Kir4.1 and Kir4.2 exist also as functional homomers. Kir4 subunits show intermediate inward rectification as homomers but much stronger rectification as heteromers with Kir5.1. Physiological functions of Kir4.1 channels include Na^+ reabsorption in the basolateral membranes of the distal convoluted tubules of the nephron; aiding in proton secretion by regulating the activity of a proton pump in gastric parietal cells; significant contributions to the endocochlear potential that is essential for proper audition; and significant contributions to the resting potential of astroglial cells in brain, spinal cord, and retina. Kir4.1 knockout mice have shown a multitude of phenotypes including deafness, epilepsy and seizures, ataxia, and hypomyelination [76].

Kir6 channels associate into octamers with the sulfonylurea (SUR) receptors (four subunits each) to form the weak inwardly rectifying K_{ATP} currents. K_{ATP} channels are inhibited by ATP and stimulated by nucleotide diphosphates (NDPs), such as ADP. They serve as metabolic sensors responding to the ATP/ADP ratio. The Kir6 subunits are responsible for the ATP inhibition, and the SUR subunits for the NDP activation. Sulfonylureas inhibit while K^+ channel openers stimulate K_{ATP} channel activity by binding to the SUR subunits. Kir6.2/SUR1 form the pancreatic K_{ATP} channel, inhibition of which causes β-cell depolarization that leads to insulin release. Kir6.2/SUR2A form the ventricular cardiac K_{ATP} channel that is activated (or less inhibited) under lower ATP/ADP ratios, such as during increased cardiac work load, hypoxia, or ischemia exerting a cardioprotective effect (shortening the action potential and limiting Ca^{2+} influx through Ca^{2+} channels). Kir6.1/

SUR2B form the vascular smooth muscle K_{ATP} channels that besides the ATP/ADP ratio, they respond to a number of vasodilators and vasoconstrictors. Glucose-sensitive hypothalamic neurons utilize either Kir6.1 or Kir6.2 complexed with SUR1 to regulate wakefulness, locomotor activity, appetite, sleep, energy conservation, feeding behavior, etc. Loss of function mutations cause excessive insulin secretion despite hypoglycemia (persistent hypoglycemia of infancy), while gain of function mutations cause reduced insulin secretion and hyperglycemia (neonatal diabetes mellitus) [76].

Kir7.1 is less homologous to the other Kir channels displaying a much lower single-channel conductance, ten times lower sensitivity to Ba^{2+} or Cs^{+} block, and inward rectification independent of $[K^{+}]_o$. The M125R mutation (Arg is conserved in all other Kir channels) normalized all three differences [49, 100]. Snowflake vitreoretinal degeneration patients show the heterozygous mutation R162W in Kir7.1. This mutation makes Kir7.1 behave like a non-selective cation channel, depolarizing the cells in which it is expressed [76].

K2P channels

The K2P family of potassium channels is responsible for background “leak” potassium current, which is operative over all physiological membrane potential ranges, unlike Kv and Kir channels. K2P channel subunits contain four transmembrane domains with two pores arranged in tandem, with the functional unit a homoor heterodimer.

TREK1 responds to a wide variety of physiological stimuli, with activation by intracellular acidosis, membrane stretch, polyunsaturated fatty acids, lysophospholipids, and volatile anesthetics. Inhibition results from increased cAMP or Gq-coupled signaling. Exogenous PIP_2 application was reported to reduce TREK1 response to various activating stimuli, including acidosis and membrane stretch.

TASK currents are responsive to low changes in extracellular pH and were recently implicated in stabilizing the adrenal zona glomerulosa membrane potential, which was depolarized in the TASK1/TASK3 knockout mouse. Brainstem TASK channels are also implicated in oxygen and CO_2 sensing [51].

Na^{+} channels

Among Na channels, strong evidence for regulation by phosphoinositides currently exists only for a non-voltage-gated sodium channel: the epithelial sodium channel (ENaC or amiloride-sensitive sodium channel). These channels are composed of three subunits: α-, β-, and γ-ENaC. Each subunit has two membrane-spanning domains, a large extracellular loop, and intracellular N- and C-termini. Analogy to the related acid sensing ion channels suggests that ENaC channels exist as a heterotrimer of the three subunits.

These channels are found on the apical membranes of various epithelia, and they especially play important roles in renal and pulmonary physiology. Passage through ENaC channels is the rate-limiting step for reabsorption of Na^{+}, and thus the channels are important for control of water homeostasis and blood pressure. In humans, loss of function mutations in ENaC are associated with pseudohypoaldosteronism type-I (PHA-I) characterized by volume depletion, hypotension, and hyperkalemia. In contrast, gain of function mutations are

associated with Liddle syndrome characterized by volume expansion, hypertension, hypokalemia, low aldosterone level, and metabolic alkalosis. In lung/airway epithelial cells, ENaC function is important for clearance of surface liquid. Loss of function mutations associated with PHA-I are additionally associated with neonatal respiratory distress syndrome due to pulmonary edema. Impaired ENaC activity is furthermore also linked to susceptibility to high-altitude pulmonary edema in patients [11].

Relevant phenotypes have also been observed for various mouse models. Knockout of the a-ENaC subunit results in lethal respiratory distress syndrome. On the other hand, certain gain of function ENaC mutations can recapitulate cystic fibrosis-like symptoms in transgenic mice by causing increased clearance of liquid from lungs and increased inflammation [11, 85].

Cl^- channels

Among Cl^- channels, evidence for regulation by phosphoinositides currently exists only for the cystic fibrosis transmembrane conductance regulator (CFTR) channel. This protein also functions as a member of the ATP-binding cassette (ABC) transporter superfamily of ATPases. It is the only known ABC transporter ATPase to also function as an ion channel. CFTR seems to be constructed from a single polypeptide containing several domains: two transmembrane domains containing six membrane-spanning helices each, two nucleotide binding domains, and a regulatory domain. Anion flow is vital for normal water movement across epithelia, and loss of function of the CFTR channel leads to cystic fibrosis characterized by thickening of mucous secretions, which impair function at various epithelial surfaces including airways, intestines, pancreatic ducts, testes, and sweat glands. Two thirds of all cystic fibrosis cases are due to the ΔF508, but over 1,000 other disease-causing mutations are also recorded. ΔF508 leads to failure of protein maturation and its eventual degradation. Many of the other mutations also lead to loss of function by truncation or by effects on open probability and conduction rate. However, most disease-causing mutations have not yet been characterized [61].

P2X receptors

The entire family of P2X receptor cation channels that are gated by extracellular ATP has been shown to be PIP_2 sensitive [232]. There are seven different P2X receptor subunits (P2X1-7) that can assemble as homo- or heterotrimers [31]. P2X receptor subunits consist of a large extracellular domain and two transmembrane helices. Both the N- and C-termini are intracellular [90]. P2X receptors have a widespread expression in the nervous system, with P2X2, 4 and 6 being the most abundant in neurons [94].

P2X1 receptors are abundantly expressed in smooth muscle cells and platelets [94]. P2X1 knockout male mice are infertile, due to a defect in purinergic neurotransmission in the vas deferens, which controls emission of sperm into the semen [94]. A severe bleeding disorder has also been linked to a single amino acid deletion in the P2X1 subunit [151]. Consistently, P2X1 knockout mice exhibit reduced thrombosis after injury of the walls of small arterioles [198].

P2X2 has a perisynaptic localization in excitatory synapses in the brain. There are presynaptic P2X2 receptors as well, which increase glutamate release onto inhibitory interneurons in the feed-forward circuit in the hippocampus [94]. In the periphery, P2X2 is important for myenteric neurotransmission, as knockout mice show impaired fEPSCs in myenteric neurons [94]. P2X2 has also a predominant role in the response to hypoxia in the carotid body, since excitation of primary afferent nerves by hypoxia is much reduced in mice lacking P2X2 [198]. Homomeric and/or heteromeric P2X2 and P2X3 receptors are essential players in taste transduction [198]. P2X2 or P2X3 knockout mice exhibit moderately diminished neural and behavioral responses to tastants, whereas double mutants show complete absence of nerve responses to tastants applied to the oral cavity.

P2X3 is implicated in neuropathic and inflammatory pain. P2X3 subunits are abundantly expressed in a subset of primary afferent neurons implicated in pain sensation, and P2X3 knockout mice exhibit greatly reduced mechanical allodynia, together with further defects in afferent sensation [94]. Moreover, P2X3 is expressed in bladder afferent nerves, and P2X3 knockout mice have also impaired ability to sense bladder filling [94].

The first described phenotype of P2X4 knockout mice was an increase in blood pressure [94] P2X4 knockout mice also show lack of flow-induced calcium and NO production in lung microvessels and decreased vasodilation. The vascular phenotype of P2X4 knockout mice generally resembles the one in endothelial nitric oxide synthase knockout mice, supporting the idea that P2X4 subunits are involved in the modulation of NO production and release. P2X4 subunits have been implicated in pain sensation as well. Tactile allodynia is much reduced when downregulating P2X4 expression in the dorsal horn, using antisense oligonucleotides [94]. Moreover, P2X4 subunit expression is increased in microglia of the dorsal horn of the spinal cord following spinal nerve ligation, a common model for neuropathic pain. P2X4 and P2X6 subunits are also found in perisynaptic locations on hippocampal CA1 and cerebellar Purkinje cells. Long-term potentiation is impaired in the hippocampus of P2X4 knockout mice [198].

P2X7 is expressed abundantly in cells of the immune system, including macrophages and microglia [31]. P2X7 seems to be critically involved in cytokine release, as P2X7 knockout mice do not release interleukin-1β in response to ATP [94]. P2X7 is also implicated in pain perception, as P2X7-deficient mice show reduced or absent behavioral responses to inflammation of the paw (chronic inflammatory pain) and tactile allodynia (neuropathic pain) [198]. Moreover, P2X7 is normally expressed in osteoclasts and osteo-blasts. Bone metabolism is impaired in mice with a P2X7 deletion, giving rise to a unique skeletal phenotype with excessive resorption of the trabecular bone [94]. Interestingly, P2X7 knockout mice have also been shown to exhibit antidepressant-like behaviors and increased responsiveness to a low dose of the antidepressant drug imipramine [6].

iGluRs

Thus far, ionotropic glutamate receptors (iGluRs) have been shown to be regulated by phosphoinositides in atypical ways. iGluRs are ligand-gated channels responsible for the vast majority of excitatory neurotransmission in the nervous system [46]. They are divided into subclasses (NMDA, AMPA, and kainate) according to their pharmacological behavior

(i.e., agonist specificity) [118]. NMDA receptors are obligate heterotetramers consisting of GluN1 (NR1) and GluN2A-D (NR2A-D) or GluN3A-B (NR3A-B) [140]. AMPA receptors subunits (GluA1-4 or GluRA-D) and kainate receptors subunits (GluK1-5 or GluR5-7) can form homotetramers, but the native receptors are most likely heterotetramers [35, 125]. The membrane topology and domain organization is common in all iGluR subunits [188]. The amino-terminal domain, implicated in subtype-specific receptor assembly and allosteric modulation, and the ligand-binding domain are extracellular. The transmembrane domain consists of three transmembrane helices (M1, M3, and M4) and a re-entrant loop (M2). The C-terminal domain is cytoplasmic.

iGluRs have well-established roles in synaptic plasticity and neuronal development [37]. Given the physiological significance of iGluRs in the nervous system, it is not surprising that they have been linked to an array of pathological conditions, including Fragile-X syndrome, schizophrenia, Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, ischemic stroke, and neuropathic pain [19, 46, 54]. iGluRs have also been implicated in depression [72] and epilepsy [156]. CNS disorders are generally considered multifactorial, and often, a specific etiology has not been established [19]. However, aberrant iGluR function has been implicated in several mouse models for CNS disorders.

NMDA receptors act as coincidence detectors at postsynaptic sites. Upon activation, they allow calcium to flow into the cell, an event that is critical for most forms of synaptic plasticity [129]. They are activated by PIP_2 through interactions that are mediated by the cytoskeletal associated protein α-actinin [137]. The cytoskeleton might also play an important role in these interactions [132]. Several mouse models for Huntington's disease have demonstrated an increase in NMDA receptor-mediated currents in striatal neurons and altered synaptic plasticity [54].

AMPA receptors mediate fast excitatory neurotransmission and are also critically involved in synaptic plasticity. Depending on their subunit composition, they are either constantly trafficked to and from the synapse (GluA2/3) or they are recruited in an activity-dependent manner (GluA1/2) [185]. It has been shown that PIP_3 regulates AMPA receptor mobility at the synapse and is necessary for maintaining AMPA receptors in the synaptic compartment [4]. Knockout mice for GluA1 have been shown to exhibit behavioral and neurochemical alterations that have been linked to major depressive disorder [34]. Also, a mouse model for Fragile-X syndrome exhibits exaggerated AMPAR-associated LTD in the CA1 region of the hippocampus and in Purkinje cells of the cerebellum [19].

Kainate receptors can be found at both pre- and postsynaptic sites. At postsynaptic sites, kainate receptors not only produce synaptic currents but also regulate neuronal excitability. Presynaptic kainate receptors are known to regulate transmitter release and affect both excitatory and inhibitory neurotransmission [156]. GluK1 knockout mice show decreased responses to capsaicin or inflammatory pain, whereas GluK2 knockout mice exhibit reduced fear memory [97]. Finally, several kainate receptor subunits have been implicated in animal models of epileptic seizures [19]. No regulation of kainate receptors by phosphoinositides has been reported yet.

Ca^{2+}-release channels

Ca^{2+} release channels include ryanodine receptors and inositol triphosphate (IP_3) receptors. These channels predominantly localize to the sarcoplasmic and endoplasmic reticula, respectively. They are considered intracellular receptors, where they participate in the release of internal calcium stores.

IP3 receptor subunits consist of a large cytoplasmic N-terminus, six membrane-spanning helices, and a short cytoplasmic C-terminus. Three different genes with various splice variants encode these subunits which then homo- or heterotetramerize to form functional channels. These channels participate in the release of intracellular Ca^{2+} stores in response to IP_3 released from hydrolysis of membrane PIP_2. While this fundamental signaling mechanism is vital to a myriad of physiological processes from learning/memory to apoptosis, no human diseases directly involving mutations of IP3 receptors are known. It is hypothesized that perhaps this is due to functional redundancy among the various isoforms and splice variants. Knockout of type 1 IP_3 receptors causes neurological defects and early death. Knockout of both type 2 and type 3 is required to generate a pancreatic acinar cell secretion mouse phenotype [58].

Ryanodine receptor (RyR) subunits are likely to be composed of four transmembrane domains with cytoplasmic termini. Three genes encode RyR subunits: RyR1 and RyR2 are found in the terminal cisternae of muscle sarcoplasmic reticulum, where they are responsible for the release of internal Ca^{2+} stores in excitation–contraction coupling; the exact role of RyR3 is unclear. RyR3 is found in all cells, RyR1 is considered the skeletal muscle isoform, and RyR2 is considered the cardiac muscle isoform, although both RyR1 and RyR2 have also been shown to be present in peripheral lymphocytes. Mutations in RyR1 and RyR2 are associated with autosomal-dominant diseases of skeletal and cardiac muscle, such as malignant hyper-thermia, central core disease, catecholaminergic polymorphic ventricular tachycardia, and arrhythmogenic right ventricular dysplasia type 2. No disease-associated mutations are known for RyR3, while $RyR3^{(-/-)}$ mice show defects in memory and learning. Knockout of RyR1 or RyR2 is lethal early in embryonic development [23].

Other channels

Gap junctions are defined as clusters of few to hundreds of tightly packed intercellular channels that allow small molecules to be directly transferred between neighboring cells [104]. The connexin family consists of 21 members in humans. Cx43 is the most widely expressed connexin, found in 35 distinct tissues [104], and it is inhibited by depletion of PIP_2 [205]. Mutations in Cx43 have been linked to the pleiotropic developmental disorder ODDD. Patients suffering from this disorder exhibit syndactyly, craniofacial abnormalities, brittle nails, hair abnormalities, conductive hearing loss, lens defects, cornea defects, abnormalities of the teeth, and occasional neurological and heart symptoms [104]. Of the described loss-of-function mutations, two affect positively charged residues (K134E and R202H).

The volume-regulated anion channel (VRAC) is mainly permeable to Cl^- under physiological conditions and is activated by classical “cell-swelling protocols” [144]. The

molecular identity of VRAC is presently unknown. VRAC is regulated by PIP_3 in mouse ventricular myocytes [219].

Transporters and exchangers

The plasma membrane Ca^{2+}-ATPase (PMCA) belongs to the P-type class of ion-motive ATPases. Its expression is ubiquitous and plays a critical role in Ca^{2+}-homeostasis in the cell. There are four isoforms of PMCA pumps (PMCA1–4), with PMCA1 and 4 expressed ubiquitously in animal cells, whereas PMCA2 and 3 have more specific expression (nervous tissue, with PMCA2 also expressed in the inner ear) [26]. The physiological role of PMCA pumps is to drive Ca^{2+} out of the cell by coupling it with hydrolysis of ATP. PMCA1 is activated in the presence of PIP_2 [33]. The phenotypes of knockout mice for PMCA1, 2, and 4 have been reported [162]. Deletion of PMCA1 is embryonic lethal, consistent with a housekeeping function of this form of the enzyme. PMCA2 knockout mice develop pronounced deafness, with defect in both vestibular and auditory systems. Several findings are consistent with an important role of PMCA2 in hearing. The major phenotype of PMCA4 is male infertility.

The Na^+/Ca^{2+} exchanger family consists of three genes (NCX1, NCX2, and NCX3). NCX1 is the dominant form found in most types of cells [18]. The Na^+/Ca^{2+} exchanger catalyzes the exchange of one intracellular Ca^{2+} with three extracellular Na^+ [38]. NCX1 activity is potentiated in the presence of PIP_2 (i.e., [78]). Human NCX1 is upregulated in pressure overload, end-stage heart failure, and senescence, and it may play a role in excitation contraction coupling [38]. Deletion of NCX1 is embryonic lethal, as the embryos do not have beating hearts. A role of NCX1 in pacemaker function has been suggested [38].

The Na^+/H^+ exchanger catalyzes the electroneutral exchange of one intracellular H^+ for an extracellular Na^+ and, as a result, regulates intracellular pH and cell volume [166]. NHE1 (SLC9A1) is ubiquitously expressed and is activated by PIP_2 [1]. NHE1 also acts as a plasma membrane anchor for cortical actin filaments [166].

The NBCe1 transporter is an electrogenic Na^+-coupled HCO_3^- that belongs to the SLC4 family of transporters [174]. The NBCe1-A variant is first characterized and is expressed primarily in kidney. Two other variants exist: NBCe1-B has widespread expression, and NBCe1-C is expressed almost exclusively in the brain. The NBCe1-A variant is activated by PIP_2 [215]. In the kidney, NBCe1-A is responsible for the reabsorption of HCO_3^- from the lumen to blood [174]. Four naturally occurring mutations of NBCe1 have been reported that cause persistent recessive renal tubular acidosis and ocular abnormalities [174]. Interestingly, two of these mutations are missense mutations that target two highly conserved arginines among the SLC4 family members.

Kv channels

Kv channels, composed of tetramers of single alpha subunits, consist of a voltage sensor coupled to a pore domain, with varying biophysical properties that allow for a large degree of heterogeneity. They contain six transmembrane domains where the first four comprise the voltage sensor, while the last two make-up the channel pore, just like in Kir channels. They are activated in response to membrane depolarization and are responsible for repolarizing

the cell following an action potential. The Kv family is composed of Kv1–Kv9, with Kv5.x, 6.x, 8.x, and 9.x composed of silent subunits, which do not localize to the membrane on their own, but must associate with a Kv1–4 family member. Kv1.1, Kv1.4, and Kv3.4 were shown to have relatively fast N-type inactivation abrogated by addition of intracellular PIP_2, presumably by immobilizing the inactivation domain [149].

Kv1.1 has been implicated in episodic ataxia, a rare disorder resulting in transient episodes of ataxia with otherwise intact neurological function. Kv1.1 knockout mice show increased incidence of spontaneous seizures, with altered hippocampal excitability and nerve conduction. The V408A Kv1.1 transgene is embryonic lethal when homozygous, whereas heterozygous mice display a similar phenotype to patients with episodic ataxia, including relief with acetazolamide treatment [88].

Kv1.3 has recently become a candidate for multiple sclerosis treatment, owing to a correlation of myelin-reactive T cells with high Kv1.3 expression. Kv1.3 knockout mice have increased basal metabolic rates compared to wild type, which may explain their reduced body weight phenotype [216].

Kv1.5 polymorphisms (P532L and R578K) can result in reduced sensitivity to the antiarrhythmic quinidine. Kv1.5 mutants have also recently been implicated in familial atrial fibrillation according to genetic analysis [105].

Kv7.x (KCNQ) channels stand on their own as therapeutic targets, owing to an extensive body of work investigating their physiological and pathophysiological role. All members of the Kv7 subfamily have been shown to be PIP_2 sensitive [229].

The role of Kv7.1 in heart is well appreciated, since mutants can cause Long QT (LQT) syndrome. Defective Kv7.1 subunit assembly can result in the Jervell and Lange–Nielsen cardioauditory syndrome. A mouse model for this syndrome was produced by disrupting the Kv7.1 gene, resulting in inner ear defects and prolonged QT intervals.

The majority of Kv7.2 channels form heteromers with Kv7.3, resulting in the Kv7.2/3 M current, a slowly activating current that arises at sub-threshold potentials. Importantly, Kv7.2/3 can be inhibited by muscarinic AChR stimulation, resulting in Gq-coupled hydrolysis of PIP_2 and subsequent closure of the channel. Kv7.2/3 is implicated in benign familial neonatal convulsions, an autosomal-dominant disorder characterized by episodic partial and complex seizures starting early in life and disappearing soon afterward.

Disruption of Kv7.4, expressed mainly in the outer hair cells of the air and the auditory nuclei of the brainstem, results in congenital deafness.

Kv7.5 has unresolved function, but may contribute to the M current. There are no known diseases resulting from Kv7.5 mutations [24].

Kv11.1 (HERG, for human ether-a-go-go related gene) is also heavily researched for its role in LQT syndrome. HERG channels have the unique characteristic of faster inactivation than activation, with subsequent recovery of inactivation that is faster than deactivation. This results in a sustained outward current as the membrane repolarizes, causing the steep slope

of phase 3 repolarization in atrial and ventricular myocytes. The Kv11.1 B isoform knockout is predisposed to sinus bradycardia [14].

CNG channels

Cyclic nucleotide-gated (CNG) are important in vision and olfaction. Retinitis pigmentosa can result from mutation of phototransduction-specific cGMP-gated channel CNGA1, while knockout mice of olfactory-specific CNGA2 display a broad phenotype of failure to mate or fight, likely due to disruption of normal olfactory physiology and response to environmental cues [15].

HCN channels

Among CNG channels are the HCN channels that are responsible for the I_f "funny" current in the heart pacemaker nodes, so-called due to their unusual property of activation by hyperpolarization from resting membrane potentials. HCN channels in the nervous system regulate rhythmic firing of pacemaking neurons, as well as contributing to routine neuronal functions. HCN channels are regulated by the cyclic nucleotides cAMP and cGMP, which serve to depolarize the half-activation voltage, essentially resulting in increased excitability for hyperpolarization-activated channels. The HCN4 knockout is embryonic lethal, presumably due to the loss of autonomic regulation of the heartbeat. The HCN2 knockout suggests that this channel may have overlapping function with HCN4, as knockout mice have a sinus dysrhythmia but maintain normal response to autonomic signals [16].

Ca^{2+}-activated K^+ channels

Ca^{2+}-activated K^+ (or K_{Ca}, Big K^+, Maxi K) channels belong to the SLO family of large conductance channels, also referred to as SLO1, and thus far they are the only member of this family shown to depend on phosphoinositides [204] (also see [169]). They can be activated either by depolarization or by intracellular Ca^{2+} alone or synergistically by both. Their predicted membrane topology resembles the Kv channel six transmembrane helices with a voltage sensor (helices 1–4) and pore (helices 5–6) domains but, in addition, has an extra helix (helix 0) that places the N-terminus extracellularly and a long cytosolic domain with two ring structures (RCK domains) and a distal region involved in the Ca^{2+}-sensing mechanism. SLO1 channels are ubiquitously expressed regulating endocrine secretions and vascular, urinary bladder, and respiratory tone [39]. In the CNS, they space bursts of Ca^{2+} action potentials (e.g., dendrites of cerebellar Purkinje cells), they underlie the fast phase of the after-hyperpolarization potential (somata of CA1 hippocampal pyramidal neurons), and they regulate synaptic transmission (in presynaptic terminals sensing Ca^{2+} influx through Ca_v channels) [181]. Malfunctions of SLO1 channels can lead to generalized epilepsy and paroxysmal dyskinesia, noise-induced hearing loss, hypertension, urinary incontinence, overactive urine bladder, and asthma [39, 181].

Ca_v channels

Ca_v channels are calcium-selective voltage-gated channels with four subunits (voltage sensor and pore domains) linked in tandem to form a functional channel. Calcium channels are critical for electrochemical signaling in eukaryotic cells and are broadly classified as L-

type, P/Q-type, N-type, R-type, and T-type channels regarding their biophysical and pharmacological characteristics.

Due to its crucial role in calcium-induced calcium release signaling, defects in L-type $Ca_v1.2$ function produce multi-organ dysfunction, best represented by Timothy syndrome, causing developmental and mental abnormalities, heart disease, hypoglycemia, immune deficiency, and autism [190].

Mutations in the neuronally restricted P/Q-type $Ca_v2.1$ can result in familial hemiplegic migraine, spinocerebellar ataxia, and episodic ataxia [64].

N-type $Ca_v2.2$ is expressed in the spinal cord and dorsal raphe nucleus, and knockout mice exhibit reduced pain sensation and aggressive behavior, consistent with their proposed roles in target cell types of ascending pain and control of aggression, respectively [96].

TRP channels

The transient receptor potential (TRP) superfamily in humans is comprised of six subfamilies: canonical (TRPC1-7), melastatin (TRPM1-8), vanilloid (TRPV1–6), ankyrin (TRPA1), polycystin (TRPP2-3 and TRPP5), and mucolipin (TRPML1-3). The subunits are composed of six transmembrane regions (S1–S6) with a pore-forming loop between S5 and S6. These subunits assemble into homo- or heterotetramers and form cation-selective channels [143]. While most TRP channels allow for the entry of Ca^{2+}, exceptions such as the TRPM4 and TRPM5 channels are permeable to monovalent cations, but not to Ca^{2+} or Mg^{2+}. On the other hand, TRPV5 and TRPV6 are highly Ca^{2+} permeable, while TRPM6 and TRPM7 are highly permeable to Mg^{2+}. Furthermore, TRPV1, TRPML1, and TRPP3 are additionally highly permeable to H^+ ions. TRP channels tend to respond to a wide variety of stimuli including ligand binding, temperature, osmolarity, mechanical forces, or voltage [146]. Given the size of this family of channels and the diversity of stimuli they respond to, it is not surprising to find them implicated in a large variety of fundamental physiologic processes.

TRPC2 is a pseudogene in humans; in a knockout mouse model, however, the processing of pheromone signals was disrupted, and the mice displayed behavioral abnormalities including defects in gender recognition. TRPC4 knockout mice exhibit altered endothelial function as well as changes in neurotransmission. Endothelium-dependent vasorelaxation as well as mechanisms for endothelial control of paracellular permeability are affected. The serotonin-induced release of GABA from thalamic interneurons is reduced in TRPC4 knockout mice. Transmission of this GABAergic signal may play a role in sleep/wake cycles or in visual processing, although relation to human disease is not yet clear. Six mutations in TRPC6 have been linked to late-onset type focal segmental glomerular sclerosis (FSGS) in humans. Three of the mutations were gain of function, while the remainder showed no evidence of altered function; this gave rise to the hypothesis that increased Ca^{2+} entry leads to Ca^{2+} overload and death of glomerular podocytes and the ensuing pathology of FSGS. TRPC6 knockout mice show an increased contractile response in vascular and tracheal smooth muscle and exhibit moderately increased blood pressures. These effects are thought to result from a compensatory upregulation of TRPC3 channels in the TRPC6 knockout mice, and

thus the importance of these channels for human diseases such as hypertension remains to be clarified.

TRPM5 knockout mice have disruptions in sweet, bitter, and umami taste perception. They also lose the temperature dependence of sweet taste. The role of TRPM5 in analogous human phenomena and its involvement in taste disorders remains to be proven. Several mutations in TRPM6 are strongly linked to hypomagnesemia with secondary hypocalcemia in humans. TRPM6 is among the Mg^{2+}-permeable TRP channels, and defects in its activity are thought to lead to impaired active uptake of Mg^{2+} in the small intestine as well as impaired Mg^{2+} reabsorption in the distal convoluted tubule of the nephron. In a zebrafish model, mutations in TRPM7 caused severe growth retardation: endochondral ossification was accelerated, while intramembranous ossification was delayed. Additional abnormalities in the mutant zebrafish include the development of kidney stones and defects in embryonic melanophores and the touch response.

TRPV1 knockout mice have been studied extensively and exhibit several interesting phenotypes. These mice exhibit impaired inflammatory thermal hyperalgesia and do not exhibit pain behavior normally elicited by pungent vanilloids or painful heat. These mice not only exhibit reduced mechanosensation and nociception but inflammation-induced enhancement in these sensory signals is also abolished. Similarly, the knockout mice exhibit decreased swelling and hypersensitivity in a model for chronic osteoarthritis. In a model of allergic contact dermatitis, the TRPV1 knockout had a more pronounced pathologic phenotype compared to wild-type mice. Finally, the knockout mice also showed changes in bladder function. The mice display a higher frequency of spontaneous low volume urine spotting along with decreased bladder stretch detection. They also are resistant to bladder overactivity in the setting of acute bladder inflammation. TRPV3 knockout mice display diminished responses to innocuous and noxious heat and also have some hair abnormalities. Several rodents bearing TRPV3 mutations in the S4-S5 linker are spontaneously hairless, and some develop symptoms of atopic dermatitis similar to the human disease. The TRPV4 knockout mice have a mild phenotype showing moderate changes in blood osmolarity and water intake. They exhibit decreased secretion of antidiuretic hormone but normal response to the hormone. TRPV5 knockout mice have impaired osteoclast function but increased osteoclast number. These mice exhibit osteoporosis possibly due to compensatory upregulation of TRPV6 and an increase in 1,25-dihydroxyvitamin D_3. TRPV6 knockout mice exhibit reduced fertility, alopecia, dermatitis, impaired intestinal Ca^{2+} uptake, and impaired renal Ca^{2+} reabsorption.

TRPA1 knockout mice show impaired pain responses to endogenous inflammatory mediators and to topical application of a variety of noxious stimuli including mustard oil, acrolein, and allicin. Knockout mice also show resistance to bradykinin-induced hyperalgesia. Mutations in the homologous gene in *Drosophila* also lead to reduced avoidance to noxious thermal, chemical, and osmotic stimuli.

Mutations in TRPP1 or TRPP2 are the cause of autosomal-dominant polycystic kidney disease in humans. Other structural abnormalities are also linked to mutations of TRPP1: heart valve defects, aneurysms, colonic diverticula, and inguinal hernias. TRPP2 mutations

can also lead to heart defects such as problems in septum formation. TRPP2 mutations in transgenic mice recapitulate many of these phenotypes: cyst formation, septal defects, whole body edema, renal failure, and early death. TRPP2$^{(-/-)}$ mice show similar defects but almost always die in utero. TRPP2$^{(+/-)}$ mice have intermediate survival but do not develop cysts or renal failure. Another knockout allele of TRPP2 resulted in the malformations mentioned above but additionally demonstrated cardiac, pulmonary, and gastric situs inversus among other laterality defects.

TRPML1 mutations are linked to mucolipidosis type IV, an autosomal recessive lysosomal storage disorder characterized by psychomotor retardation, ocular abnormalities, agenesis of the corpus callosum, hypoferremia, and achlorhydria. The mechanism by which TRPML1 mutations lead to defects in lipid storage and lysosome function remains unclear. Knockout of TRPML3 is lethal, but several mutations have been characterized in mice. These mice have defects in maturation of stereocilia and melanocyte function leading to an overall phenotype which includes deafness, vestibular defects, and a characteristic tri-color coat [146].

Channelopathies and PIP_2

Mutations in the genes encoding ion channel proteins may lead to altered channel function and thus underlie channelopathies. Increasing evidence suggests that some disease-causing mutations exert their effects on channel activity by altering channel-PIP_2 interactions. As mentioned above, the interaction between PIP_2 and channel residues is thought to involve a largely electrostatic component: positively charged side chains of channel residues near the inner membrane leaflet are attracted to the negatively charged phosphoinositol headgroups of PIP_2 [55, 89]. However, uncharged residues near these critical PIP_2-interacting regions can also alter apparent PIP_2 affinity of the channel, possibly through allosteric mechanisms involving nearby positively charged residues (e.g., [122]). Thus, a variety of charged and uncharged residues in critical PIP_2 interacting regions of various channels has been found to both alter PIP_2 affinity and also lead to disease.

Mutations in the KCNJ2 gene leading to loss of function in Kir2.1 have been tied to the Andersen–Tawil syndrome (ATS) [47]. ATS occurs either sporadically or in an autosomal-dominant pattern and is characterized by periodic paralysis, cardiac arrhythmias, and dysmorphic features, although the presence and severity of these features can vary considerably [157]. Several of the KCNJ2 mutations underlying the syndrome have been shown in vitro to impair channel-PIP_2 interactions and thus decrease its open probability [122]. Kir2.1 residues, when mutated, have been found to both underlie ATS in patients and shown to alter channel-PIP2 interaction in vitro include R67, R189, R218, G300, E303, and R312 [47, 122]. Another Kir2.1 residue potentially linked to ATS, L217, has not directly been tested in vitro for effects on PIP_2 affinity, but its location within the critical PIP_2-interacting region of the channel and especially its proximity to the PIP_2-interacting R218 residue led its discoverers to hypothesize that it too leads to a loss of function phenotype by disrupting channel-PIP_2 interactions [44].

Mutations in the KCNJ1 gene leading to a loss of function in Kir1.1 have been tied to hyperprostaglandin E syndrome (HPS), the antenatal form of Bartter syndrome [86, 182, 184]. HPS is an autosomal recessive disease characterized by polyhydramnios, premature delivery, hypokalemic alkalosis, and hypercalciuria [182]. Several of the KCNJ1 mutations underlying HPS have been shown in vitro to also impair channel-PIP_2 interactions and thus decrease Kir1.1 open probability [122]. Residues potentially tied to HPS that have also been shown to affect Kir1.1–PIP_2 interactions include R311 (equivalent to Kir2.1 R312 discussed above), C49, I51, A214, and L220 [122] (but also see [167]).

Some mutations in KCNJ11 causing a loss of function in Kir6.2 have been tied to congenital hyperinsulinism (CHI) [66, 113, 168]. Loss of Kir6.2 currents leads to increased excitability of pancreatic β cells and thus an increased secretion of insulin. A few of the mutations linked to CHI can be mapped to the putative PIP_2 binding site on the Kir6.2 channel [68]. Residues that have been found to be mutated in patients with CHI that also have been shown to be important for channel–PIP_2 interactions include F55, R301, and K67 [68, 112, 113, 168].

Many mutations in KCNQ1 causing a loss of function in Kv7.1 have been linked to LQT syndrome. The pathogenic mechanism behind at least a few of these mutations appears to be disruption of channel–PIP_2 interactions. Residues important for PIP_2 binding that have also been found to be mutated in LQT syndrome patients include R243H, R539W, and R555C [152].

Ryan et al. recently reported the discovery of KCNJ18 and its product Kir2.6, which were previously unknown. Kir2.6 is primarily expressed in skeletal muscle and shares 96–99% amino acid identity with Kir2.2. Several mutations in this gene were identified in patients with thyrotoxic hypokalemic periodic paralysis (TPP). TPP is a sporadic disorder, which occurs in a subset of thyrotoxic individuals. It is characterized by episodic muscle weakness (clinically similar to the periodic paralysis found in ATS) and hypokalemia [157, 178]. A few of the Kir2.6 mutations found in TPP patients were also shown to alter channel–PIP_2 interactions. The R205H and K366R mutations turned out to be gain of function mutations and appeared to increase PIP_2 affinity. Increased Kir2.6 currents would tend to hyperpolarize the cell and decrease excitability, possibly leading to weakness/paralysis.

These examples establish a pattern whereby the alteration of channel–PIP_2 interactions can be the underlying pathogenic mechanism for either gain or loss of function mutations associated with channelopathies. Disease-associated mutations that can be mapped to channel residues adjacent to the intracellular leaflet of the membrane may potentially exert their effects through modulation of channel–PIP_2 interactions. It should be noted that although mutation of a residue may alter the channel–PIP_2 interaction, it may play additional roles such as participation in intersubunit hydrogen bonds which could also affect gating.

Concluding remarks

In the last decade, we have witnessed an impressive number of ion channels that employ quite diverse mechanisms of gating, ion selectivity, and permeation to display similar dependence of their activity on the plasma membrane phosphoinositide PIP_2. Channel (basic

residues)–PIP_2 (negative phosphate) interactions exhibit a strong electrostatic component, but non-charged residues can also affect channel–PIP_2 interactions either directly or allosterically. The fundamental and widespread role of PIP_2 in controlling channel activity begs the question of whether already identified channelopathies of ion channels, whose activity depends on this phosphoinositide, operate in part or in whole by altering channel–PIP_2 interactions. Moreover, dysregulation of the phosphoinositide pathway can result in either too much or too little PIP_2. It is likely that in such cases along with the many other important functions that phosphoinositides control, ion channel activity could become dysregulated, giving rise to channelopathies. It feels that we have only scratched the tip of the iceberg, and the realization of the fundamental importance of PIP_2 in ion channel function in the past decade will guide us in the coming decade to an appreciation of the ways in which disruption of channel–PIP_2 interactions due to either channel or phosphoinositide malfunctions can lead to disease.

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References

1. Aharonovitz O, Zaun HC, Balla T, York JD, Orlowski J, Grinstein S. Intracellular pH regulation by Na+/H+ exchange requires phosphatidylinositol 4, 5-bisphosphate. J Cell Biol. 2000; 150:213–224. [PubMed: 10893269]
2. Akopian AN, Ruparel NB, Jeske NA, Hargreaves KM. Transient receptor potential TRPA1 channel desensitization in sensory neurons is agonist dependent and regulated by TRPV1-directed internalization. J Physiol. 2007; 583:175–193. [PubMed: 17584831]
3. Albert AP, Saleh SN, Large WA. Inhibition of native TRPC6 channel activity by phosphatidylinositol 4, 5-bisphosphate in mesenteric artery myocytes. J Physiol. 2008; 586:3087–3095. [PubMed: 18467363]
4. Arendt KL, Royo M, Fernandez-Monreal M, Knafo S, Petrok CN, Martens JR, Esteban JA. PIP3 controls synaptic function by maintaining AMPA receptor clustering at the postsynaptic membrane. Nat Neurosci. 2010; 13:36–44. [PubMed: 20010819]
5. Asteggiano C, Berberian G, Beauge L. Phosphatidyl inositol-4, 5-bisphosphate bound to bovine cardiac Na+/Ca2+ exchanger displays a MgATP regulation similar to that of the exchange fluxes. Eur J Biochem. 2001; 268:437–442. [PubMed: 11168380]
6. Basso AM, Bratcher NA, Harris RR, Jarvis MF, Decker MW, Rueter LE. Behavioral profile of P2X7 receptor knockout mice in animal models of depression and anxiety: Relevance for neuropsychiatric disorders. Behav Brain Res. 2009; 198:83–90. [PubMed: 18996151]
7. Baukrowitz T, Schulte U, Oliver D, Herlitze S, Krauter T, Tucker SJ, Ruppersberg JP, Fakler B. PIP2 and PIP as determinants for ATP inhibition of KATP channels. Science. 1998; 282:1141–1144. [PubMed: 9804555]
8. Berman DE, Dall'Armi C, Voronov SV, McIntire LB, Zhang H, Moore AZ, Staniszewski A, Arancio O, Kim TW, Di Paolo G. Oligomeric amyloid-beta peptide disrupts phosphatidylinositol-4, 5-bisphosphate metabolism. Nat Neurosci. 2008; 11:547–554. [PubMed: 18391946]
9. Bernier L, Ase AR, Chevallier S, Blais D, Zhao Q, Boue-Grabot E, Logothetis D, Seguela P. Phosphoinositides regulate P2X4 ATP-gated channels through direct interactions. J Neurosci. 2008; 28:12938–12945. [PubMed: 19036987]

10. Bernier L, Ase AR, Tong X, Hamel E, Blais D, Zhao Q, Logothetis DE, Séguéla P. Direct modulation of P2X1 receptor-channels by the lipid phosphatidylinositol 4, 5-bisphosphate. Mol Pharmacol. 2008; 74:785–792. [PubMed: 18523136]
11. Bhalla V, Hallows KR. Mechanisms of ENaC regulation and clinical implications. J Am Soc Nephrol. 2008; 19:1845–1854. [PubMed: 18753254]
12. Bian J, Cui J, McDonald TV. HERG K+channel activity is regulated by changes in phosphatidyl inositol 4, 5-bisphosphate. Circ Res. 2001; 89:1168–1176. [PubMed: 11739282]
13. Bian JS, Kagan A, McDonald TV. Molecular analysis of PIP2 regulation of HERG and IKr. Am J Physiol Heart Circ Physiol. 2004; 287:H2154–H2163. [PubMed: 15231497]
14. Bian JS, McDonald TV. Phosphatidylinositol 4, 5-bisphosphate interactions with the HERG K(+) channel. Pflugers Arch. 2007; 455:105–113. [PubMed: 17622552]
15. Biel M, Michalakis S. Function and dysfunction of CNG channels: insights from channelopathies and mouse models. Mol Neurobiol. 2007; 35:266–277. [PubMed: 17917115]
16. Biel M, Wahl-Schott C, Michalakis S, Zong X. Hyperpolarization-activated cation channels: from genes to function. Physiol Rev. 2009; 89:847–885. [PubMed: 19584315]
17. Bielas SL, Silhavy JL, Brancati F, Kisseleva MV, Al-Gazali L, Sztriha L, Bayoumi RA, Zaki MS, Abdel-Aleem A, Rosti RO, Kayserili H, Swistun D, Scott LC, Bertini E, Boltshauser E, Fazzi E, Travaglini L, Field SJ, Gayral S, Jacoby M, Schurmans S, Dallapiccola B, Majerus PW, Valente EM, Gleeson JG. Mutations in INPP5E, encoding inositol polyphosphate-5-phosphatase E, link phosphatidyl inositol signaling to the ciliopathies. Nat Genet. 2009; 41:1032–1036. [PubMed: 19668216]
18. Blaustein MP, Lederer WJ. Sodium/calcium exchange: its physiological implications. Physiol Rev. 1999; 79:763–854. [PubMed: 10390518]
19. Bowie D. Ionotropic glutamate receptors & CNS disorders. CNS Neurol Disord Drug Targets. 2008; 7:129–143. [PubMed: 18537642]
20. Brady JD, Rich ED, Martens JR, Karpen JW, Varnum MD, Brown RL. Interplay between PIP3 and calmodulin regulation of olfactory cyclic nucleotide-gated channels. Proc Natl Acad Sci USA. 2006; 103:15635–15640. [PubMed: 17032767]
21. Brauchi S, Orta G, Mascayano C, Salazar M, Raddatz N, Urbina H, Rosenmann E, Gonzalez-Nilo F, Latorre R. Dissection of the components for PIP2 activation and thermosensation in TRP channels. Proc Natl Acad Sci USA. 2007; 104:10246–10251. [PubMed: 17548815]
22. Bright SR, Rich ED, Varnum MD. Regulation of human cone cyclic nucleotide-gated channels by endogenous phospholipids and exogenously applied phosphatidylinositol 3, 4, 5-trisphosphate. Mol Pharmacol. 2007; 71:176–183. [PubMed: 17018579]
23. Brini M. Ryanodine receptor defects in muscle genetic diseases. Biochem Biophys Res Commun. 2004; 322:1245–1255. [PubMed: 15336972]
24. Brown DA, Passmore GM. Neural KCNQ (Kv7) channels. Br J Pharmacol. 2009; 156:1185–1195. [PubMed: 19298256]
25. Burke MA, Mutharasan RK, Ardehali H. The sulfonylurea receptor, an atypical ATP-binding cassette protein, and its regulation of the KATP channel. Circ Res. 2008; 102:164–176. [PubMed: 18239147]
26. Carafoli E, Brini M. Calcium pumps: structural basis for and mechanism of calcium transmembrane transport. Curr Opin Chem Biol. 2000; 4:152–161. [PubMed: 10742184]
27. Chemin J, Girard C, Duprat F, Lesage F, Romey G, Lazdunski M. Mechanisms underlying excitatory effects of group I metabotropic glutamate receptors via inhibition of 2P domain K +channels. EMBO J. 2003; 22:5403–5411. [PubMed: 14532113]
28. Chemin J, Patel AJ, Duprat F, Lauritzen I, Lazdunski M, Honore E. A phospholipid sensor controls mechanogating of the K+channel TREK-1. EMBO J. 2005; 24:44–53. [PubMed: 15577940]
29. Chemin J, Patel AJ, Duprat F, Sachs F, Lazdunski M, Honore E. Up- and down-regulation of the mechano-gated K(2P) channel TREK-1 by PIP (2) and other membrane phospholipids. Pflugers Arch. 2007; 455:97–103. [PubMed: 17384962]
30. Cheng WWL, Enkvetchakul D, Nichols CG. KirBac1.1: it's an inward rectifying potassium channel. J Gen Physiol. 2009; 133:295–305. [PubMed: 19204189]

31. Chizh BA, Illes P. P2X receptors and nociception. Pharmacol Rev. 2001; 53:553–568. [PubMed: 11734618]
32. Cho H, Youm JB, Ryu SY, Earm YE, Ho WK. Inhibition of acetylcholine-activated K(+) currents by U73122 is mediated by the inhibition of PIP(2)-channel interaction. Br J Pharmacol. 2001; 134:1066–1072. [PubMed: 11682455]
33. Choquette D, Hakim G, Filoteo AG, Plishker GA, Bostwick JR, Penniston JT. Regulation of plasma membrane Ca2+ ATPases by lipids of the phosphatidylinositol cycle. Biochem Biophys Res Commun. 1984; 125:908–915. [PubMed: 6097254]
34. Chourbaji S, Vogt MA, Fumagalli F, Sohr R, Frasca A, Brandwein C, Hortnagl H, Riva MA, Sprengel R, Gass P. AMPA receptor subunit 1 (GluR-A) knockout mice model the glutamate hypothesis of depression. FASEB J. 2008; 22:3129–3134. [PubMed: 18492725]
35. Christensen JK, Paternain AV, Selak S, Ahring PK, Lerma J. A mosaic of functional kainate receptors in hippocampal interneurons. J Neurosci. 2004; 24:8986–8993. [PubMed: 15483117]
36. Chuang HH, Prescott ED, Kong H, Shields S, Jordt SE, Basbaum AI, Chao MV, Julius D. Bradykinin and nerve growth factor release the capsaicin receptor from PtdIns(4, 5)P2-mediated inhibition. Nature. 2001; 411:957–962. [PubMed: 11418861]
37. Cohen S, Greenberg ME. Communication between the synapse and the nucleus in neuronal development, plasticity, and disease. Annu Rev Cell Dev Biol. 2008; 24:183–209. [PubMed: 18616423]
38. Conway SJ, Kruzynska-Frejtag A, Wang J, Rogers R, Kneer PL, Chen H, Creazzo T, Menick DR, Koushik SV. Role of sodium-calcium exchanger (Ncx1) in embryonic heart development: a transgenic rescue? Ann NY Acad Sci. 2002; 976:268–281. [PubMed: 12502569]
39. Cui J, Yang H, Lee US. Molecular mechanisms of BK channel activation. Cell Mol Life Sci. 2009; 66:852–875. [PubMed: 19099186]
40. Cukras CA, Jeliazkova I, Nichols CG. Structural and functional determinants of conserved lipid interaction domains of inward rectifying Kir6.2 channels. J Gen Physiol. 2002; 119:581–591. [PubMed: 12034765]
41. Czirjak G, Petheo GL, Spat A, Enyedi P. Inhibition of TASK-1 potassium channel by phospholipase C. Am J Physiol Cell Physiol. 2001; 281:C700–C708. [PubMed: 11443069]
42. Dai Y, Wang S, Tominaga M, Yamamoto S, Fukuoka T, Higashi T, Kobayashi K, Obata K, Yamanaka H, Noguchi K. Sensitization of TRPA1 by PAR2 contributes to the sensation of inflammatory pain. J Clin Invest. 2007; 117:1979–1987. [PubMed: 17571167]
43. Daniels RL, Takashima Y, McKemy DD. Activity of the neuronal cold sensor TRPM8 is regulated by phospholipase C via the phospholipid phosphoinositol 4, 5-bisphosphate. J Biol Chem. 2009; 284:1570–1582. [PubMed: 19019830]
44. Davies NP, Imbrici P, Fialho D, Herd C, Bilsland LG, Weber A, Mueller R, Hilton-Jones D, Ealing J, Boothman BR, Giunti P, Parsons LM, Thomas M, Manzur AY, Jurkat-Rott K, Lehmann-Horn F, Chinnery PF, Rose M, Kullmann DM, Hanna MG. Andersen-Tawil syndrome: new potassium channel mutations and possible phenotypic variation. Neurology. 2005; 65:1083–1089. [PubMed: 16217063]
45. Decher N, Gonzalez T, Streit A, Sachse F, Renigunta V, Soom M, Heinemann S, Daut J, Sanguinetti M. Structural determinants of Kvbeta1.3-induced channel inactivation: a hairpin modulated by PIP2. EMBO J. 2008; 27:3164–3174. [PubMed: 18987637]
46. Dingledine R, Borges K, Bowie D, Traynelis SF. The glutamate receptor ion channels. Pharmacol Rev. 1999; 51:7–61. [PubMed: 10049997]
47. Donaldson MR, Jensen JL, Tristani-Firouzi M, Tawil R, Bendahhou S, Suarez WA, Cobo AM, Poza JJ, Behr E, Wagstaff J, Szepetowski P, Pereira S, Mozaffar T, Escolar DM, Fu YH, Ptacek LJ. PIP2 binding residues of Kir2.1 are common targets of mutations causing Andersen syndrome. Neurology. 2003; 60:1811–1816. [PubMed: 12796536]
48. Dong K, Tang L, MacGregor GG, Hebert SC. Localization of the ATP/phosphatidylinositol 4, 5 diphosphate-binding site to a 39-amino acid region of the carboxyl terminus of the atp-regulated K + channel Kir1.1. J Biol Chem. 2002; 277:49366–49373. [PubMed: 12381730]

49. Doring F, Derst C, Wischmeyer E, Karschin C, Schneggenburger R, Daut J, Karschin A. The epithelial inward rectifier channel Kir7.1 displays unusual K+permeation properties. J Neurosci. 1998; 18:8625–8636. [PubMed: 9786970]
50. Du X, Zhang H, Lopes C, Mirshahi T, Rohacs T, Logothetis DE. Characteristic interactions with phosphatidylinositol 4, 5-bisphosphate determine regulation of Kir channels by diverse modulators. J Biol Chem. 2004; 279:37271–37281. [PubMed: 15155739]
51. Duprat F, Lauritzen I, Patel A, Honore E. The TASK background K2P channels: chemo- and nutrient sensors. Trends Neurosci. 2007; 30:573–580. [PubMed: 17945357]
52. Enkvetchakul D, Nichols CG. Gating mechanism of KATP channels: function fits form. J Gen Physiol. 2003; 122:471–480. [PubMed: 14581579]
53. Fan Z, Makielski JC. Anionic phospholipids activate ATP-sensitive potassium channels. J Biol Chem. 1997; 272:5388–5395. [PubMed: 9038137]
54. Fan MMY, Raymond LA. N-Methyl-D-aspartate (NMDA) receptor function and excitotoxicity in Huntington's disease. Prog Neurobiol. 2007; 81:272–293. [PubMed: 17188796]
55. Ferguson KM, Lemmon MA, Schlessinger J, Sigler PB. Structure of the high affinity complex of inositol trisphosphate with a phospholipase C pleckstrin homology domain. Cell. 1995; 83:1037–1046. [PubMed: 8521504]
56. Filomatori CV, Rega AF. On the mechanism of activation of the plasma membrane Ca2+-ATPase by ATP and acidic phospholipids. J Biol Chem. 2003; 278:22265–22271. [PubMed: 12660230]
57. Ford CP, Stemkowski PL, Smith PA. Possible role of phosphatidylinositol 4, 5, bisphosphate in luteinizing hormone releasing hormone-mediated M-current inhibition in bullfrog sympathetic neurons. Eur J NeuroSci. 2004; 20:2990–2998. [PubMed: 15579153]
58. Foskett JK, White C, Cheung KH, Mak DO. Inositol trisphosphate receptor Ca2+ release channels. Physiol Rev. 2007; 87:593–658. [PubMed: 17429043]
59. Fujiwara Y, Kubo Y. Regulation of the desensitization and ion selectivity of ATP-gated P2X2 channels by phosphoinositides. J Physiol. 2006; 576:135–149. [PubMed: 16857707]
60. Furukawa T, Yamane T, Terai T, Katayama Y, Hiraoka M. Functional linkage of the cardiac ATP-sensitive K+channel to the actin cytoskeleton. Pflugers Arch. 1996; 431:504–512. [PubMed: 8596692]
61. Gadsby DC, Vergani P, Csanady L. The ABC protein turned chloride channel whose failure causes cystic fibrosis. Nature. 2006; 440:477–483. [PubMed: 16554808]
62. Gamper N, Reznikov V, Yamada Y, Yang J, Shapiro MS. Phosphotidylinositol 4, 5-bisphosphate signals underlie receptor-specific Gq/11-mediated modulation of N-type Ca2+ channels. J Neurosci. 2004; 24:10980–10992. [PubMed: 15574748]
63. Gamper N, Shapiro MS. Regulation of ion transport proteins by membrane phosphoinositides. Nat Rev Neurosci. 2007; 8:921–934. [PubMed: 17971783]
64. Gazulla J, Tintore M. P/Q-type voltage-dependent calcium channels in neurological disease. Neurologia. 2007; 22:511–516. [PubMed: 17573560]
65. Glouchankova L, Krishna UM, Potter BVL, Falck JR, Bezprozvanny I. Association of the inositol (1, 4, 5)-trisphosphate receptor ligand binding site with phosphatidylinositol (4, 5)-bisphosphate and adenophostin A. Mol Cell Biol Res Commun. 2000; 3:153–158. [PubMed: 10860863]
66. Gloyn AL, Siddiqui J, Ellard S. Mutations in the genes encoding the pancreatic beta-cell KATP channel subunits Kir6.2 (KCNJ11) and SUR1 (ABCC8) in diabetes mellitus and hyperinsulinism. Hum Mutat. 2006; 27:220–231. [PubMed: 16416420]
67. Goldstein SAN, Bayliss DA, Kim D, Lesage F, Plant LD, Rajan S. International union of pharmacology. LV. Nomenclature and molecular relationships of two-P potassium channels. Pharmacol Rev. 2005; 57:527–540. [PubMed: 16382106]
68. Haider S, Tarasov AI, Craig TJ, Sansom MS, Ashcroft FM. Identification of the PIP2-binding site on Kir6.2 by molecular modelling and functional analysis. EMBO J. 2007; 26:3749–3759. [PubMed: 17673911]
69. Halstead JR, Jalink K, Divecha N. An emerging role for PtdIns(4, 5)P2-mediated signalling in human disease. Trends Pharmacol Sci. 2005; 26:654–660. [PubMed: 16253350]
70. Harmar AJ, Hills RA, Rosser EM, Jones M, Buneman OP, Dunbar DR, Greenhill SD, Hale VA, Sharman JL, Bonner TI, Catterall WA, Davenport AP, Delagrange P, Dollery CT, Foord SM,

Gutman GA, Laudet V, Neubig RR, Ohlstein EH, Olsen RW, Peters J, Pin J, Ruffolo RR, Searls DB, Wright MW, Spedding M. IUPHAR-DB: the IUPHAR database of G protein-coupled receptors and ion channels. Nucleic Acids Res. 2009; 37:D680–D685. [PubMed: 18948278]

71. Haruna T, Yoshida H, Nakamura TY, Xie LH, Otani H, Ninomiya T, Takano M, Coetzee WA, Horie M. α1-Adrenoceptor-mediated breakdown of phosphatidylinositol 4, 5-bisphosphate inhibits pinacidil-activated ATP-sensitive K+ currents in rat ventricular myocytes. Circ Res. 2002; 91:232–239. [PubMed: 12169649]
72. Hashimoto K. Emerging role of glutamate in the pathophysiology of major depressive disorder. Brain Res Rev. 2009; 61:105–123. [PubMed: 19481572]
73. He Z, Feng S, Tong Q, Hilgemann DW, Philipson KD. Interaction of PIP2 with the XIP region of the cardiac Na/Ca exchanger. Am J Physiol Cell Physiol. 2000; 278:C661–C666. [PubMed: 10751315]
74. Hernandez CC, Falkenburger B, Shapiro MS. Affinity for phosphatidylinositol 4, 5-bisphosphate determines muscarinic agonist sensitivity of Kv7 K+channels. J Gen Physiol. 2009; 134:437–448. [PubMed: 19858360]
75. Hernandez CC, Zaika O, Shapiro MS. A carboxy-terminal inter-helix linker as the site of phosphatidylinositol 4, 5-bisphosphate action on Kv7 (M-type) K+channels. J Gen Physiol. 2008; 132:361–381. [PubMed: 18725531]
76. Hibino H, Inanobe A, Furutani K, Murakami S, Findlay I, Kurachi Y. Inwardly rectifying potassium channels: their structure, function, and physiological roles. Physiol Rev. 2010; 90:291–366. [PubMed: 20086079]
77. Hilgemann DW. Regulation and deregulation of cardiac Na(+)-Ca2+ exchange in giant excised sarcolemmal membrane patches. Nature. 1990; 344:242–245. [PubMed: 2314460]
78. Hilgemann DW, Ball R. Regulation of cardiac Na+, Ca2+ exchange and KATP potassium channels by PIP2. Science. 1996; 273:956–959. [PubMed: 8688080]
79. Himmel B, Nagel G. Protein kinase-independent activation of CFTR by phosphatidylinositol phosphates. EMBO Rep. 2004; 5:85–90. [PubMed: 14710196]
80. Hirdes W, Horowitz LF, Hille B. Muscarinic modulation of erg potassium current. J Physiol. 2004; 559:67–84. [PubMed: 15235086]
81. Hirono M, Denis CS, Richardson GP, Gillespie PG. Hair cells require phosphatidylinositol 4, 5-bisphosphate for mechanical transduction and adaptation. Neuron. 2004; 44:309–320. [PubMed: 15473969]
82. Ho IH, Murrell-Lagnado RD. Molecular mechanism for sodium-dependent activation of G protein-gated K+channels. J Physiol. 1999; 520(3):645–651. [PubMed: 10545132]
83. Huang CL. Complex roles of PIP2 in the regulation of ion channels and transporters. Am J Physiol Renal Physiol. 2007; 293:F1761–F1765. [PubMed: 17928411]
84. Huang CL, Feng S, Hilgemann DW. Direct activation of inward rectifier potassium channels by PIP2 and its stabilization by Gbetagamma. Nature. 1998; 391:803–806. [PubMed: 9486652]
85. Hummler E, Planes C. Importance of ENaC-mediated sodium transport in alveolar fluid clearance using genetically-engineered mice. Cell Physiol Biochem. 2010; 25:63–70. [PubMed: 20054145]
86. International Collaborative Study Group for Bartter-like Syndromes. Mutations in the gene encoding the inwardly-rectifying renal potassium channel, ROMK, cause the antenatal variant of Bartter syndrome: evidence for genetic heterogeneity. Hum Mol Genet. 1997; 6:17–26. [PubMed: 9002665]
87. Jardin I, Redondo PC, Salido GM, Rosado JA. Phosphatidylinositol 4, 5-bisphosphate enhances store-operated calcium entry through hTRPC6 channel in human platelets. Biochim Biophys Acta. 2008; 1783:84–97. [PubMed: 17719101]
88. Jen JC, Graves TD, Hess EJ, Hanna MG, Griggs RC, Baloh RW, CINCH investigators. Primary episodic ataxias: diagnosis, pathogenesis and treatment. Brain. 2007; 130:2484–2493. [PubMed: 17575281]
89. Kavran JM, Klein DE, Lee A, Falasca M, Isakoff SJ, Skolnik EY, Lemmon MA. Specificity and promiscuity in phosphoinositide binding by pleckstrin homology domains. J Biol Chem. 1998; 273:30497–30508. [PubMed: 9804818]

90. Kawate T, Michel JC, Birdsong WT, Gouaux E. Crystal structure of the ATP-gated P2X(4) ion channel in the closed state. Nature. 2009; 460:592–598. [PubMed: 19641588]
91. Kaznacheyeva E, Zubov A, Nikolaev A, Alexeenko V, Bezprozvanny I, Mozhayeva GN. Plasma membrane calcium channels in human carcinoma A431 cells are functionally coupled to inositol 1, 4, 5-trisphosphate receptor-phosphatidylinositol 4, 5-bisphosphate complexes. J Biol Chem. 2000; 275:4561–4564. [PubMed: 10671480]
92. Kellenberger S, Schild L. Epithelial sodium channel/Degenerin family of ion channels: A variety of functions for a shared structure. Physiol Rev. 2002; 82:735–767. [PubMed: 12087134]
93. Khakh BS, Burnstock G, Kennedy C, King BF, North RA, Séguéla P, Voigt M, Humphrey PPA. International Union of Pharmacology. XXIV. Current status of the nomenclature and properties of P2X receptors and their subunits. Pharmacol Rev. 2001; 53:107–118. [PubMed: 11171941]
94. Khakh BS, North RA. P2X receptors as cell-surface ATP sensors in health and disease. Nature. 2006; 442:527–532. [PubMed: 16885977]
95. Kim D, Cavanaugh EJ, Simkin D. Inhibition of transient receptor potential A1 channel by phosphatidylinositol-4, 5-bisphosphate. Am J Physiol Cell Physiol. 2008; 295:C92–C99. [PubMed: 18495815]
96. Kim C, Jeon D, Kim YH, Lee CJ, Kim H, Shin HS. Deletion of N-type Ca(2+) channel Ca(v)2.2 results in hyperaggressive behaviors in mice. J Biol Chem. 2009; 284:2738–2745. [PubMed: 19004821]
97. Ko S, Zhao MG, Toyoda H, Qiu CS, Zhuo M. Altered behavioral responses to noxious stimuli and fear in glutamate receptor 5 (GluR5)- or GluR6-deficient mice. J Neurosci. 2005; 25:977–984. [PubMed: 15673679]
98. Kobayashi M, Muroyama A, Ohizumi Y. Phosphatidylinositol 4, 5-bisphosphate enhances calcium release from sarcoplasmic reticulum of skeletal muscle. Biochem Biophys Res Commun. 1989; 163:1487–1491. [PubMed: 2476988]
99. Kobrinsky E, Mirshahi T, Zhang H, Jin T, Logothetis DE. Receptor-mediated hydrolysis of plasma membrane messenger PIP2 leads to K+-current desensitization. Nat Cell Biol. 2000; 2:507–514. [PubMed: 10934471]
100. Krapivinsky G, Medina I, Eng L, Krapivinsky L, Yang Y, Clapham DE. A novel inward rectifier K+channel with unique pore properties. Neuron. 1998; 20:995–1005. [PubMed: 9620703]
101. Krauter T, Ruppersberg JP, Baukrowitz T. Phospholipids as modulators of K(ATP) channels: distinct mechanisms for control of sensitivity to sulphonylureas, K(+) channel openers, and ATP. Mol Pharmacol. 2001; 59:1086–1093. [PubMed: 11306691]
102. Kunzelmann K, Bachhuber T, Regeer R, Markovich D, Sun J, Schreiber R. Purinergic inhibition of the epithelial Na+ transport via hydrolysis of PIP2. FASEB J. 2005; 19:142–143. [PubMed: 15504951]
103. Kwon Y, Hofmann T, Montell C. Integration of phosphoinositide- and calmodulin-mediated regulation of TRPC6. Mol Cell. 2007; 25:491–503. [PubMed: 17317623]
104. Laird DW. Life cycle of connexins in health and disease. Biochem J. 2006; 394:527–543. [PubMed: 16492141]
105. Lawson K, McKay NG. Modulation of potassium channels as a therapeutic approach. Curr Pharm Des. 2006; 12:459–470. [PubMed: 16472139]
106. Lechner SG, Hussl S, Schicker KW, Drobny H, Boehm S. Presynaptic inhibition via a phospholipase C- and phosphatidylinositol bisphosphate-dependent regulation of neuronal Ca2+ channels. Mol Pharmacol. 2005; 68:1387–1396. [PubMed: 16099842]
107. Lee J, Cha SK, Sun TJ, Huang CL. PIP2 activates TRPV5 and releases its inhibition by intracellular Mg2+ J Gen Physiol. 2005; 126:439–451. [PubMed: 16230466]
108. Lei Q, Talley EM, Bayliss DA. Receptor-mediated inhibition of G protein-coupled inwardly rectifying potassium channels involves Galpha q family subunits, phospholipase C, and a readily diffusible messenger. J Biol Chem. 2001; 276:16720–16730. [PubMed: 11279027]
109. Lemonnier L, Trebak M, Putney JW Jr. Complex regulation of the TRPC3, 6 and 7 channel subfamily by diacylglycerol and phosphatidylinositol-4, 5-bisphosphate. Cell Calcium. 2008; 43:506–514. [PubMed: 17942152]

110. Leung YM, Zeng WZ, Liou HH, Solaro CR, Huang CL. Phosphatidylinositol 4, 5-bisphosphate and intracellular pH regulate the ROMK1 potassium channel via separate but interrelated mechanisms. J Biol Chem. 2000; 275:10182–10189. [PubMed: 10744702]
111. Li Y, Gamper N, Hilgemann DW, Shapiro MS. Regulation of Kv7 (KCNQ) K+channel open probability by phosphatidylinositol 4, 5-bisphosphate. J Neurosci. 2005; 25:9825–9835. [PubMed: 16251430]
112. Lin YW, Bushman JD, Yan FF, Haidar S, MacMullen C, Ganguly A, Stanley CA, Shyng SL. Destabilization of ATP-sensitive potassium channel activity by novel KCNJ11 mutations identified in congenital hyperinsulinism. J Biol Chem. 2008; 283:9146–9156. [PubMed: 18250167]
113. Lin YW, MacMullen C, Ganguly A, Stanley CA, Shyng SL. A novel KCNJ11 mutation associated with congenital hyperinsulinism reduces the intrinsic open probability of beta-cell ATP-sensitive potassium channels. J Biol Chem. 2006; 281:3006–3012. [PubMed: 16332676]
114. Liou HH, Zhou SS, Huang CL. Regulation of ROMK1 channel by protein kinase A via a phosphatidylinositol 4, 5-bisphosphate-dependent mechanism. Proc Natl Acad Sci USA. 1999; 96:5820–5825. [PubMed: 10318968]
115. Liu D, Liman ER. Intracellular Ca2+ and the phospholipid PIP2 regulate the taste transduction ion channel TRPM5. Proc Natl Acad Sci USA. 2003; 100:15160–15165. [PubMed: 14657398]
116. Liu B, Qin F. Functional control of cold- and menthol-sensitive TRPM8 ion channels by phosphatidylinositol 4, 5-bisphosphate. J Neurosci. 2005; 25:1674–1681. [PubMed: 15716403]
117. Liu B, Zhang C, Qin F. Functional recovery from desensitization of vanilloid receptor TRPV1 requires resynthesis of phosphatidylinositol 4, 5-bisphosphate. J Neurosci. 2005; 25:4835–4843. [PubMed: 15888659]
118. Lodge D. The history of the pharmacology and cloning of ionotropic glutamate receptors and the development of idiosyncratic nomenclature. Neuropharmacology. 2009; 56:6–21. [PubMed: 18765242]
119. Logothetis DE, Jin T, Lupyan D, Rosenhouse-Dantsker A. Phosphoinositide-mediated gating of inwardly rectifying K(+) channels. Pflugers Arch. 2007; 455:83–95. [PubMed: 17520276]
120. Logothetis DE, Lupyan D, Rosenhouse-Dantsker A. Diverse Kir modulators act in close proximity to residues implicated in phosphoinositide binding. J Physiol. 2007; 582:953–965. [PubMed: 17495041]
121. Lopes CM, Rohacs T, Czirjak G, Balla T, Enyedi P, Logothetis DE. PIP2 hydrolysis underlies agonist-induced inhibition and regulates voltage gating of two-pore domain K+channels. J Physiol. 2005; 564:117–129. [PubMed: 15677683]
122. Lopes CM, Zhang H, Rohacs T, Jin T, Yang J, Logothetis DE. Alterations in conserved Kir channel-PIP2 interactions underlie channelopathies. Neuron. 2002; 34:933–944. [PubMed: 12086641]
123. Loussouarn G, Park KH, Bellocq C, Baro I, Charpentier F, Escande D. Phosphatidylinositol-4, 5-bisphosphate, PIP2, controls KCNQ1/KCNE1 voltage-gated potassium channels: a functional homology between voltage-gated and inward rectifier K+channels. EMBO J. 2003; 22:5412–5421. [PubMed: 14532114]
124. Loussouarn G, Pike LJ, Ashcroft FM, Makhina EN, Nichols CG. Dynamic sensitivity of ATP-sensitive K+channels to ATP. J Biol Chem. 2001; 276:29098–29103. [PubMed: 11395495]
125. Lu W, Shi Y, Jackson AC, Bjorgan K, During MJ, Sprengel R, Seeburg PH, Nicoll RA. Subunit composition of synaptic AMPA receptors revealed by a single-cell genetic approach. Neuron. 2009; 62:254–268. [PubMed: 19409270]
126. Lukacs V, Thyagarajan B, Varnai P, Balla A, Balla T, Rohacs T. Dual regulation of TRPV1 by phosphoinositides. J Neurosci. 2007; 27:7070–7080. [PubMed: 17596456]
127. Lupu VD, Kaznacheyeva E, Krishna UM, Falck JR, Bezprozvanny I. Functional coupling of phosphatidylinositol 4, 5-bisphosphate to inositol 1, 4, 5-trisphosphate receptor. J Biol Chem. 1998; 273:14067–14070. [PubMed: 9603901]
128. Lyall V, Phan TT, Ren Z, Mummalaneni S, Melone P, Mahavadi S, Murthy KS, DeSimone JA. Regulation of the putative TRPV1t salt taste receptor by phosphatidylinositol 4, 5-bisphosphate. J Neurophysiol. 2010; 103:1337–1349. doi:10.1152/jn.00883.2009. [PubMed: 20032236]

129. Lynch MA. Long-term potentiation and memory. Physiol Rev. 2004; 84:87–136. [PubMed: 14715912]
130. Ma HP, Saxena S, Warnock DG. Anionic phospholipids regulate native and expressed epithelial sodium channel (ENaC). J Biol Chem. 2002; 277:7641–7644. [PubMed: 11809744]
131. MacGregor GG, Dong K, Vanoye CG, Tang L, Giebisch G, Hebert SC. Nucleotides and phospholipids compete for binding to the C terminus of KATP channels. Proc Natl Acad Sci USA. 2002; 99:2726–2731. [PubMed: 11880626]
132. Mandal M, Yan Z. Phosphatidylinositol (4, 5)-bisphosphate regulation of N-methyl-D-aspartate receptor channels in cortical neurons. Mol Pharmacol. 2009; 76:1349–1359. [PubMed: 19770351]
133. Marker CL, Cintora SC, Roman MI, Stoffel M, Wickman K. Hyperalgesia and blunted morphine analgesia in G protein-gated potassium channel subunit knockout mice. Neuro-Report. 2002; 13:2509–2513.
134. Marker CL, Stoffel M, Wickman K. Spinal G-protein-gated K+channels formed by GIRK1 and GIRK2 subunits modulate thermal nociception and contribute to morphine analgesia. J Neurosci. 2004; 24:2806–2812. [PubMed: 15028774]
135. Matsushita Y, Ohya S, Suzuki Y, Itoda H, Kimura T, Yamamura H, Imaizumi Y. Inhibition of Kv1.3 potassium current by phosphoinositides and stromal-derived factor-1α in Jurkat T cells. Am J Physiol Cell Physiol. 2009; 296:C1079–C1085. [PubMed: 19295169]
136. Meyer T, Wellner-Kienitz M-C, Biewald A, Bender K, Eickel A, Pott L. Depletion of phosphatidylinositol 4, 5-bisphosphate by activation of phospholipase C-coupled receptors causes slow inhibition but not desensitization of G protein-gated inward rectifier K+current in atrial myocytes. J Biol Chem. 2001; 276:5650–5658. [PubMed: 11104770]
137. Michailidis IE, Helton TD, Petrou VI, Mirshahi T, Ehlers MD, Logothetis DE. Phosphatidylinositol-4, 5-bisphosphate regulates NMDA receptor activity through α-actinin. J Neurosci. 2007; 27:5523–5532. [PubMed: 17507574]
138. Michailidis IE, Zhang Y, Yang J. The lipid connection-regulation of voltage-gated Ca(2+) channels by phosphoinosi-tides. Pflugers Arch. 2007; 455:147–155. [PubMed: 17541627]
139. Mo G, Bernier LP, Zhao Q, Chabot-Dore AJ, Ase AR, Logothetis D, Cao CQ, Seguela P. Subtype-specific regulation of P2X3 and P2X2/3 receptors by phosphoinositides in peripheral nociceptors. Mol Pain. 2009; 5:47. [PubMed: 19671169]
140. Monyer H, Sprengel R, Schoepfer R, Herb A, Higuchi M, Lomeli H, Burnashev N, Sakmann B, Seeburg PH. Heteromeric NMDA receptors: molecular and functional distinction of subtypes. Science. 1992; 256:1217–1221. [PubMed: 1350383]
141. Nawaz S, Kippert A, Saab AS, Werner HB, Lang T, Nave KA, Simons M. Phosphatidylinositol 4, 5-bisphosphate-dependent interaction of myelin basic protein with the plasma membrane in oligodendroglial cells and its rapid perturbation by elevated calcium. J Neurosci. 2009; 29:4794–4807. [PubMed: 19369548]
142. Niggli V, Adunyah ES, Carafoli E. Acidic phospholipids, unsaturated fatty acids, and limited proteolysis mimic the effect of calmodulin on the purified erythrocyte Ca2+-ATPase. J Biol Chem. 1981; 256:8588–8592. [PubMed: 6455424]
143. Nilius B. TRP channels in disease. Biochim Biophys Acta. 2007; 1772:805–812. [PubMed: 17368864]
144. Nilius B, Droogmans G. Ion channels and their functional role in vascular endothelium. Physiol Rev. 2001; 81:1415–1459. [PubMed: 11581493]
145. Nilius B, Mahieu F, Prenen J, Janssens A, Owsianik G, Vennekens R, Voets T. The Ca2+-activated cation channel TRPM4 is regulated by phosphatidylinositol 4, 5-biphosphate. EMBO J. 2006; 25:467–478. [PubMed: 16424899]
146. Nilius B, Owsianik G, Voets T, Peters JA. Transient receptor potential cation channels in disease. Physiol Rev. 2007; 87:165–217. [PubMed: 17237345]
147. Noel J, Roux D, Pouyssegur J. Differential localization of Na+/H+exchanger isoforms (NHE1 and NHE3) in polarized epithelial cell lines. J Cell Sci. 1996; 109:929–939. [PubMed: 8743940]

148. Ohizumi Y, Hirata Y, Suzuki A, Kobayashi M. Two novel types of calcium release from skeletal sarcoplasmic reticulum by phosphatidylinositol 4, 5-biphosphate. Can J Physiol Pharmacol. 1999; 77:276–285. [PubMed: 10535676]

149. Oliver D, Lien CC, Soom M, Baukrowitz T, Jonas P, Fakler B. Functional conversion between A-Type and delayed rectifier K+channels by membrane lipids. Science. 2004; 304:265–270. [PubMed: 15031437]

150. Otsuguro K, Tang J, Tang Y, Xiao R, Freichel M, Tsvilovskyy V, Ito S, Flockerzi V, Zhu MX, Zholos AV. Isoform-specific inhibition of TRPC4 channel by phosphatidylinositol 4, 5-bisphosphate. J Biol Chem. 2008; 283:10026–10036. [PubMed: 18230622]

151. Oury C, Toth-Zsamboki E, Van Geet C, Thys C, Wei L, Nilius B, Vermylen J, Hoylaerts MF. A natural dominant negative P2X1 receptor due to deletion of a single amino acid residue. J Biol Chem. 2000; 275:22611–22614. [PubMed: 10816552]

152. Park KH, Piron J, Dahimene S, Merot J, Baro I, Escande D, Loussouarn G. Impaired KCNQ1-KCNE1 and phosphatidylinositol-4, 5-bisphosphate interaction underlies the long QT syndrome. Circ Res. 2005; 96:730–739. [PubMed: 15746441]

153. Pegan S, Arrabit C, Zhou W, Kwiatkowski W, Collins A, Slesinger PA, Choe S. Cytoplasmic domain structures of Kir2.1 and Kir3.1 show sites for modulating gating and rectification. Nat Neurosci. 2005; 8:279–287. [PubMed: 15723059]

154. Pian P, Bucchi A, Decostanzo A, Robinson RB, Siegelbaum SA. Modulation of cyclic nucleotide-regulated HCN channels by PIP(2) and receptors coupled to phospholipase C. Pflugers Arch. 2007; 455:125–145. [PubMed: 17605039]

155. Pian P, Bucchi A, Robinson RB, Siegelbaum SA. Regulation of gating and rundown of HCN hyperpolarization-activated channels by exogenous and endogenous PIP2. J Gen Physiol. 2006; 128:593–604. [PubMed: 17074978]

156. Pinheiro P, Mulle C. Kainate receptors. Cell Tissue Res. 2006; 326:457–482. [PubMed: 16847640]

157. Plaster NM, Tawil R, Tristani-Firouzi M, Canun S, Bendahhou S, Tsunoda A, Donaldson MR, Iannaccone ST, Brunt E, Barohn R, Clark J, Deymeer F, George AL Jr, Fish FA, Hahn A, Nitu A, Ozdemir C, Serdaroglu P, Subramony SH, Wolfe G, Fu YH, Ptacek LJ. Mutations in Kir2.1 cause the developmental and episodic electrical phenotypes of Andersen's syndrome. Cell. 2001; 105:511–519. [PubMed: 11371347]

158. Pochynyuk O, Bugaj V, Vandewalle A, Stockand JD. Purinergic control of apical plasma membrane PI(4, 5)P2 levels sets ENaC activity in principal cells. Am J Physiol Renal Physiol. 2008; 294:F38–F46. [PubMed: 17913833]

159. Pochynyuk O, Staruschenko A, Tong Q, Medina J, Stockand JD. Identification of a functional phosphatidylinositol 3, 4, 5-trisphosphate binding site in the epithelial Na+channel. J Biol Chem. 2005; 280:37565–37571. [PubMed: 16154997]

160. Pochynyuk O, Tong Q, Medina J, Vandewalle A, Staruschenko A, Bugaj V, Stockand JD. Molecular determinants of PI(4, 5)P2 and PI(3, 4, 5)P3 regulation of the epithelial Na+channel. J Gen Physiol. 2007; 130:399–413. [PubMed: 17893193]

161. Posada V, Beauge L, Berberian G. Maximal Ca2+i stimulation of cardiac Na+/Ca2+ exchange requires simultaneous alkalinization and binding of PtdIns-4, 5–P2 to the exchanger. Biol Chem. 2007; 388:281–288. [PubMed: 17338635]

162. Prasad V, Okunade GW, Miller ML, Shull GE. Pheno-types of SERCA and PMCA knockout mice. Biochem Biophys Res Commun. 2004; 322:1192–1203. [PubMed: 15336967]

163. Pravetoni M, Wickman K. Behavioral characterization of mice lacking GIRK/Kir3 channel subunits. Genes Brain Behav. 2008; 7:523–531. [PubMed: 18194467]

164. Prescott ED, Julius D. A modular PIP2 binding site as a determinant of capsaicin receptor sensitivity. Science. 2003; 300:1284–1288. [PubMed: 12764195]

165. Priori SG, Napolitano C. Cardiac and skeletal muscle disorders caused by mutations in the intracellular Ca2+ release channels. J Clin Invest. 2005; 115:2033–2038. [PubMed: 16075044]

166. Putney LK, Denker SP, Barber DL. The changing face of the Na+/H+exchanger, NHE1: structure, regulation, and cellular actions. Annu Rev Pharmacol Toxicol. 2002; 42:527–552. [PubMed: 11807182]

167. Rapedius M, Haider S, Browne KF, Shang L, Sansom MS, Baukrowitz T, Tucker SJ. Structural and functional analysis of the putative pH sensor in the Kir1.1 (ROMK) potassium channel. EMBO Rep. 2006; 7:611–616. [PubMed: 16641935]
168. Reimann F, Huopio H, Dabrowski M, Proks P, Gribble FM, Laakso M, Otonkoski T, Ashcroft FM. Characterisation of new KATP-channel mutations associated with congenital hyperinsulinism in the Finnish population. Diabetologia. 2003; 46:241–249. [PubMed: 12627323]
169. Rittenhouse AR. PIP2 PIP2 hooray for maxi K+ J Gen Physiol. 2008; 132:5–8. [PubMed: 18562503]
170. Robbins J, Marsh SJ, Brown DA. Probing the regulation of M (Kv7) potassium channels in intact neurons with membrane-targeted peptides. J Neurosci. 2006; 26:7950–7961. [PubMed: 16870740]
171. Rohacs T, Chen J, Prestwich GD, Logothetis DE. Distinct specificities of inwardly rectifying K(+) channels for phosphoinositides. J Biol Chem. 1999; 274:36065–36072. [PubMed: 10593888]
172. Rohacs T, Lopes CM, Jin T, Ramdya PP, Molnar Z, Logothetis DE. Specificity of activation by phosphoinositides determines lipid regulation of Kir channels. Proc Natl Acad Sci USA. 2003; 100:745–750. [PubMed: 12525701]
173. Rohacs T, Lopes CM, Michailidis I, Logothetis DE. PI(4, 5)P2 regulates the activation and desensitization of TRPM8 channels through the TRP domain. Nat Neurosci. 2005; 8:626–634. [PubMed: 15852009]
174. Romero MF, Fulton CM, Boron WF. The SLC4 family of HCO 3—transporters. Pflugers Arch. 2004; 447:495–509. [PubMed: 14722772]
175. Rosenhouse-Dantsker A, Logothetis DE. Molecular characteristics of phosphoinositide binding. Pflugers Arch. 2007; 455:45–53. [PubMed: 17588168]
176. Rousset M, Cens T, Gouin-Charnet A, Scamps F, Charnet P. Ca2+ and phosphatidylinositol 4, 5-bisphosphate stabilize a Gβγ-sensitive state of CaV2 Ca2+ channels. J Biol Chem. 2004; 279:14619–14630. [PubMed: 14722074]
177. Runnels LW, Yue L, Clapham DE. The TRPM7 channel is inactivated by PIP(2) hydrolysis. Nat Cell Biol. 2002; 4:329–336. [PubMed: 11941371]
178. Ryan DP, da Silva MR, Soong TW, Fontaine B, Donaldson MR, Kung AW, Jongjaroenprasert W, Liang MC, Khoo DH, Cheah JS, Ho SC, Bernstein HS, Maciel RM, Brown RH Jr, Ptacek LJ. Mutations in potassium channel Kir2.6 cause susceptibility to thyrotoxic hypokalemic periodic paralysis. Cell. 2010; 140:88–98. [PubMed: 20074522]
179. Saleh SN, Albert AP, Large WA. Obligatory role for phosphatidylinositol 4, 5-bisphosphate in activation of native TRPC1 store-operated channels in vascular myocytes. J Physiol. 2009; 587:531–540. [PubMed: 19047197]
180. Saleh SN, Albert AP, Large WA. Activation of native TRPC1/C5/C6 channels by endothelin-1 is mediated by both PIP3 and PIP2 in rabbit coronary artery myocytes. J Physiol. 2009; 587:5361–5375. [PubMed: 19770190]
181. Salkoff L, Butler A, Ferreira G, Santi C, Wei A. High-conductance potassium channels of the SLO family. Nat Rev Neurosci. 2006; 7:921–931. [PubMed: 17115074]
182. Schulte U, Hahn H, Konrad M, Jeck N, Derst C, Wild K, Weidemann S, Ruppersberg JP, Fakler B, Ludwig J. pH gating of ROMK (Kir1.1) channels: control by an Arg-Lys-Arg triad disrupted in antenatal Bartter syndrome. Proc Natl Acad Sci USA. 1999; 96:15298–15303. [PubMed: 10611379]
183. Schulze D, Krauter T, Fritzenschaft H, Soom M, Baukrowitz T. Phosphatidylinositol 4, 5-bisphosphate (PIP2) modulation of ATP and pH sensitivity in Kir channels. A tale of an active and a silent PIP2 site in the N terminus. J Biol Chem. 2003; 278:10500–10505. [PubMed: 12514171]
184. Schwalbe RA, Bianchi L, Accili EA, Brown AM. Functional consequences of ROMK mutants linked to antenatal Bartter's syndrome and implications for treatment. Hum Mol Genet. 1998; 7:975–980. [PubMed: 9580661]
185. Shepherd JD, Huganir RL. The cell biology of synaptic plasticity: AMPA receptor trafficking. Annu Rev Cell Dev Biol. 2007; 23:613–643. [PubMed: 17506699]

186. Shyng SL, Cukras CA, Harwood J, Nichols CG. Structural determinants of PIP(2) regulation of inward rectifier K(ATP) channels. J Gen Physiol. 2000; 116:599–608. [PubMed: 11055989]

187. Shyng SL, Nichols CG. Membrane phospholipid control of nucleotide sensitivity of KATP channels. Science. 1998; 282:1138–1141. [PubMed: 9804554]

188. Sobolevsky AI, Rosconi MP, Gouaux E. X-ray structure, symmetry and mechanism of an AMPA-subtype glutamate receptor. Nature. 2009; 462:745–756. [PubMed: 19946266]

189. Soom M, Schonherr R, Kubo Y, Kirsch C, Klinger R, Heinemann SH. Multiple PIP2 binding sites in Kir2.1 inwardly rectifying potassium channels. FEBS Lett. 2001; 490:49–53. [PubMed: 11172809]

190. Splawski I, Timothy KW, Sharpe LM, Decher N, Kumar P, Bloise R, Napolitano C, Schwartz PJ, Joseph RM, Condouris K, Tager-Flusberg H, Priori SG, Sanguinetti MC, Keating MT. Ca(V)1.2 calcium channel dysfunction causes a multi-system disorder including arrhythmia and autism. Cell. 2004; 119:19–31. [PubMed: 15454078]

191. Staruschenko A, Pochynyuk O, Vandewalle A, Bugaj V, Stockand JD. Acute regulation of the epithelial Na+channel by phosphatidylinositide 3-OH kinase signaling in native collecting duct principal cells. J Am Soc Nephrol. 2007; 18:1652–1661. [PubMed: 17442787]

192. Stein AT, Ufret-Vincenty CA, Hua L, Santana LF, Gordon SE. Phosphoinositide 3-kinase binds to TRPV1 and mediates NGF-stimulated TRPV1 trafficking to the plasma membrane. J Gen Physiol. 2006; 128:509–522. [PubMed: 17074976]

193. Suh BC, Hille B. Recovery from muscarinic modulation of M current channels requires phosphatidylinositol 4, 5-bisphosphate synthesis. Neuron. 2002; 35:507–520. [PubMed: 12165472]

194. Suh BC, Hille B. Regulation of ion channels by phosphatidylinositol 4, 5-bisphosphate. Curr Opin Neurobiol. 2005; 15:370–378. [PubMed: 15922587]

195. Suh BC, Hille B. PIP2 is a necessary cofactor for ion channel function: how and why? Annu Rev Biophys. 2008; 37:175–195. [PubMed: 18573078]

196. Suh BC, Inoue T, Meyer T, Hille B. Rapid chemically induced changes of PtdIns(4, 5)P2 gate KCNQ ion channels. Science. 2006; 314:1454–1457. [PubMed: 16990515]

197. Sui JL, Petit-Jacques J, Logothetis DE. Activation of the atrial KACh channel by the γγ subunits of G proteins or intracellular Na+ions depends on the presence of phosphatidylinositol phosphates. Proc Natl Acad Sci USA. 1998; 95:1307–1312. [PubMed: 9448327]

198. Surprenant A, North RA. Signaling at purinergic P2X receptors. Annu Rev Physiol. 2009; 71:333–359. [PubMed: 18851707]

199. Thyagarajan B, Benn BS, Christakos S, Rohacs T. Phospholipase C-mediated regulation of transient receptor potential vanilloid 6 channels: implications in active intestinal Ca2+ transport. Mol Pharmacol. 2009; 75:608–616. [PubMed: 19073818]

200. Thyagarajan B, Lukacs V, Rohacs T. Hydrolysis of phosphatidylinositol 4, 5-bisphosphate mediates calcium-induced inactivation of TRPV6 channels. J Biol Chem. 2008; 283:14980–14987. [PubMed: 18390907]

201. Tong Q, Gamper N, Medina JL, Shapiro MS, Stockand JD. Direct activation of the epithelial Na +channel by phosphatidylinositol 3, 4, 5-trisphosphate and phosphatidylinositol 3, 4-bisphosphate produced by phosphoinositide 3-OH kinase. J Biol Chem. 2004; 279:22654–22663. [PubMed: 15028718]

202. Tong Q, Stockand JD. Receptor tyrosine kinases mediate epithelial Na+channel inhibition by epidermal growth factor. Am J Physiol Renal Physiol. 2005; 288:F150–F161. [PubMed: 15454394]

203. Trebak M, Lemonnier L, DeHaven WI, Wedel BJ, Bird GS, Putney JW Jr. Complex functions of phosphatidylinositol 4, 5-bisphosphate in regulation of TRPC5 cation channels. Pflugers Arch. 2009; 457:757–769. [PubMed: 18665391]

204. Vaithianathan T, Bukiya A, Liu J, Liu P, Asuncion-Chin M, Fan Z, Dopico A. Direct regulation of BK channels by phosphatidylinositol 4, 5-bisphosphate as a novel signaling pathway. J Gen Physiol. 2008; 132:13–28. [PubMed: 18562499]

205. van Zeijl L, Ponsioen B, Giepmans BNG, Ariaens A, Postma FR, Varnai P, Balla T, Divecha N, Jalink K, Moolenaar WH. Regulation of connexin43 gap junctional communication by phosphatidylinositol 4, 5-bisphosphate. J Cell Biol. 2007; 177:881–891. [PubMed: 17535964]

206. Varnai P, Thyagarajan B, Rohacs T, Balla T. Rapidly inducible changes in phosphatidylinositol 4, 5-bisphosphate levels influence multiple regulatory functions of the lipid in intact living cells. J Cell Biol. 2006; 175:377–382. [PubMed: 17088424]

207. Vemuri R, Philipson KD. Phospholipid composition modulates the Na+-Ca2+ exchange activity of cardiac sarco-lemma in reconstituted vesicles. Biochim Biophys Acta. 1988; 937:258–268. [PubMed: 3276350]

208. Vicinanza M, D'Angelo G, Di Campli A, De Matteis MA. Phosphoinositides as regulators of membrane trafficking in health and disease. Cell Mol Life Sci. 2008; 65:2833–2841. [PubMed: 18726176]

209. Vohra J. The long QT syndrome. Heart Lung Circ. 2007; 16:S5–S12. [PubMed: 17627884]

210. Voronov SV, Frere SG, Giovedi S, Pollina EA, Borel C, Zhang H, Schmidt C, Akeson EC, Wenk MR, Cimasoni L, Arancio O, Davisson MT, Antonarakis SE, Gardiner K, De Camilli P, Di Paolo G. Synaptojanin 1-linked phosphoinositide dyshomeostasis and cognitive deficits in mouse models of Down's syndrome. Proc Natl Acad Sci USA. 2008; 105:9415–9420. [PubMed: 18591654]

211. Wei AD, Gutman GA, Aldrich R, Chandy KG, Grissmer S, Wulff H. International Union of pharmacology. LII. Nomenclature and molecular relationships of calcium-activated potassium channels. Pharmacol Rev. 2005; 57:463–472. [PubMed: 16382103]

212. Winks JS, Hughes S, Filippov AK, Tatulian L, Abogadie FC, Brown DA, Marsh SJ. Relationship between membrane phosphatidylinositol-4, 5-bisphosphate and receptor-mediated inhibition of native neuronal M channels. J Neurosci. 2005; 25:3400–3413. [PubMed: 15800195]

213. Womack KB, Gordon SE, He F, Wensel TG, Lu CC, Hilgemann DW. Do phosphatidylinositides modulate vertebrate phototransduction? J Neurosci. 2000; 20:2792–2799. [PubMed: 10751430]

214. Wu L, Bauer CS, Zhen XG, Xie C, Yang J. Dual regulation of voltage-gated calcium channels by PtdIns(4, 5)P2. Nature. 2002; 419:947–952. [PubMed: 12410316]

215. Wu J, McNicholas CM, Bevensee MO. Phosphatidylinositol 4, 5-bisphosphate (PIP2) stimulates the electrogenic Na/HCO3 cotransporter NBCe1-A expressed in *Xenopus* oocytes. Proc Natl Acad Sci USA. 2009; 106:14150–14155. [PubMed: 19667194]

216. Wulff H, Zhorov BS. K+channel modulators for the treatment of neurological disorders and autoimmune diseases. Chem Rev. 2008; 108:1744–1773. [PubMed: 18476673]

217. Xie LH, Horie M, Takano M. Phospholipase C-linked receptors regulate the ATP-sensitive potassium channel by means of phosphatidylinositol 4, 5-bisphosphate metabolism. Proc Natl Acad Sci USA. 1999; 96:15292–15297. [PubMed: 10611378]

218. Xie LH, John SA, Ribalet B, Weiss JN. Phosphatidylinositol-4, 5-bisphosphate (PIP2) regulation of strong inward rectifier Kir2.1 channels: multilevel positive cooperativity. J Physiol. 2008; 586:1833–1848. [PubMed: 18276733]

219. Yamamoto S, Ichishima K, Ehara T. Regulation of volume-regulated outwardly rectifying anion channels by phosphatidylinositol 3, 4, 5-trisphosphate in mouse ventricular cells. Biomed Res. 2008; 29:307–315. [PubMed: 19129674]

220. Yang Z, Xu H, Cui N, Qu Z, Chanchevalap S, Shen W, Jiang C. Biophysical and molecular mechanisms underlying the modulation of heteromeric Kir4.1-Kir5.1 channels by CO2 and pH. J Gen Physiol. 2000; 116:33–45. [PubMed: 10871638]

221. Yao J, Qin F. Interaction with phosphoinositides confers adaptation onto the TRPV1 pain receptor. PLoS Biol. 2009; 7:e46. [PubMed: 19243225]

222. Yaradanakul A, Feng S, Shen C, Lariccia V, Lin MJ, Yang J, Kang TM, Dong P, Yin HL, Albanesi JP, Hilgemann DW. Dual control of cardiac Na^{+}–Ca^{2+} exchange by PIP2: electro-physiological analysis of direct and indirect mechanisms. J Physiol. 2007; 582:991–1010. [PubMed: 17540705]

223. Yue G, Malik B, Yue G, Eaton DC. Phosphatidylinositol 4, 5-bisphosphate (PIP2) stimulates epithelial sodium channel activity in A6 cells. J Biol Chem. 2002; 277:11965–11969. [PubMed: 11812779]

224. Zaika O, Lara LS, Gamper N, Hilgemann DW, Jaffe DB, Shapiro MS. Angiotensin II regulates neuronal excitability via phosphatidylinositol 4, 5-bisphosphate-dependent modulation of Kv7 (M-type) K+channels. J Physiol. 2006; 575:49–67. [PubMed: 16777936]

225. Zeng WZ, Li XJ, Hilgemann DW, Huang CL. Protein kinase C inhibits ROMK1 channel activity via a phosphatidylinositol 4, 5-bisphosphate-dependent mechanism. J Biol Chem. 2003; 278:16852–16856. [PubMed: 12615924]

226. Zeng WZ, Liou HH, Krishna UM, Falck JR, Huang CL. Structural determinants and specificities for ROMK1-phosphoinositide interaction. Am J Physiol Renal Physiol. 2002; 282:F826–F834. [PubMed: 11934692]

227. Zhainazarov AB, Spehr M, Wetzel CH, Hatt H, Ache BW. Modulation of the olfactory CNG channel by Ptdlns(3, 4, 5)P3. J Membr Biol. 2004; 201:51–57. [PubMed: 15635812]

228. Zhang ZR, Chou CF, Wang J, Liang YY, Ma HP. Anionic phospholipids differentially regulate the epithelial sodium channel (ENaC) by interacting with α, β, and γ ENaC subunits. Pflugers Arch. 2010; 459:377–387. [PubMed: 19763606]

229. Zhang H, Craciun LC, Mirshahi T, Rohacs T, Lopes CM, Jin T, Logothetis DE. PIP(2) activates KCNQ channels, and its hydrolysis underlies receptor-mediated inhibition of M currents. Neuron. 2003; 37:963–975. [PubMed: 12670425]

230. Zhang H, He C, Yan X, Mirshahi T, Logothetis DE. Activation of inwardly rectifying K +channels by distinct PtdIns (4, 5)P2 interactions. Nat Cell Biol. 1999; 1:183–188. [PubMed: 10559906]

231. Zhang Z, Okawa H, Wang Y, Liman ER. Phosphatidylinositol 4, 5-bisphosphate rescues TRPM4 channels from desensitization. J Biol Chem. 2005; 280:39185–39192. [PubMed: 16186107]

232. Zhao Q, Logothetis DE, Seguela P. Regulation of ATP-gated P2X receptors by phosphoinositides. Pflugers Arch. 2007; 455:181–185. [PubMed: 17479282]

233. Zhao Q, Yang M, Ting AT, Logothetis DE. PIP_2 regulates the ionic current of P2X receptors and P2X7-mediated cell death. Channels (Austin). 2007; 1:46–55. [PubMed: 19151591]

234. Zhen XG, Xie C, Yamada Y, Zhang Y, Doyle C, Yang J. A single amino acid mutation attenuates rundown of voltage-gated calcium channels. FEBS Lett. 2006; 580:5733–5738. [PubMed: 17010345]

235. Zolles G, Klocker N, Wenzel D, Weisser-Thomas J, Fleischmann BK, Roeper J, Fakler B. Pacemaking by HCN channels requires interaction with phosphoinositides. Neuron. 2006; 52:1027–1036. [PubMed: 17178405]

Table 1

Phosphoinositide (PIP)-sensitive channels

Channel	Tissue distribution	References on PIP-sensitive channels
Kir channels		
Kir1.1 (ROMK1)	Kidney>skeletal muscle>pancreas>spleen> heart=brain>liver [70]	[48, 53, 84, 110, 114, 122, 131, 172, 183, 225, 226]
Kir2.1 (IRK1)	Forebrain, skeletal muscle, heart, macrophage cells, aortic endothelial cells [70]	[50, 53, 84, 122, 153, 171, 172, 189, 230]
Kir 2.2 (IRK2)	Heart, forebrain, cerebellum, skeletal muscle, kidney [70]	[172]
Kir2.3 (IRK3)	Heart, hippocampus, amygdala, caudate nucleus, thalamus, kidney [70]	[50,172]
Kir2.4 (IRK4)	Retina, heart, striatum [70]	[172]
Kir2.6 (IRK6)	Skeletal muscle	[178] [178]
Kir3.2 (GIRK2)	Brain, pancreas, testis [70]	[84]
Kir3.1/3.2 (GIRK1/2)	Brain [70]	[82]
Kir3.1/3.4 (GIRK1/4)	Heart atria [70]	[32, 84, 99, 108, 136, 171, 172, 197]
Kir3.4-S143T (GIRK4*)	Experimental construct	[99, 172, 230]
Kir4.1	Forebrain, cerebellum, striatum, kidney, retina [70]	[172]
Kir4.2	Kidney, pancreas>lung>prostate, testes, leukocytes [70]	[172]
Kir4.1/Kir5.1	Brainstem nuclei, kidney [70, 220]	[220]
Kir6.1	Heart, ovary, adrenal gland>skeletal muscle, lung, brain, stomach, colon, testis, thyroid, pancreatic islet cells>kidney, liver, small intestine, pituitary gland [70]	[131]
Kir6.2-Δ36	Experimental construct	[7, 131, 172]
Kir6.2/SUR1	Brain, pancreas [25, 70]	[7, 40, 53, 124, 172, 186, 187]
Kir6.2/SUR2A	Heart [25, 70]	[53, 71, 78, 101, 172, 183, 217]
Kir6.2/SUR2B	Vascular smooth muscle cells [25, 70]	[53]
Kir7.1	(Human) small intestine>stomach, kidney, brain, thyroid, choroid plexus, retinal pigment epithelium (rat) lung, testis [70]	[172]
KirBac1.1	Bacteria	[30]
K2P channels		
K_{2P}2.1 (TREK1)	Brain, heart [67]	[28, 29, 121]
K_{2P}3.1 (TASK1)	Brain, heart, lung, kidney, pancreas, others [67]	[27, 28, 41, 121]
K_{2P}4.1 (TRAAK)	Brain, kidney, small intestine, placenta, prostate [67]	[121]
K_{2P}9.1 (TASK3)	Brain [67]	[27, 121]
Na^+ channels		
ENaC (α/β/γ)	Kidney, lung, gastrointestinal tract and skin [92]	[102, 130, 158–160, 191, 201, 202, 223, 228]
Cl^- channels		
CFTR	Heart, exocrine glands (pancreas, airways, gastrointestinal tract and sweat glands) [79]	[79]
P2X receptors (ATP-gated)		
P2X1	Smooth muscle, brain, cerebellum, dorsal horn spinal neurons and platelels [93]	[10, 233]

Channel	Tissue distribution	References on PIP-sensitive channels
P2X2	Nervous system (widespread) [93]	[59, 139, 233]
P2X3	Sensory neurons [93]	[139, 233]
P2X2/3	Sensory neurons [93]	[139]
P2X4	CNS synapses [93]	[9, 233]
P2X5	Brain, heart, spinal cord, adrenal medulla, thymus and lymphocytes [93]	[233]
P2X7	Macrophages, lymphocytes, microglia, osteoclasts, osteoblasts [31, 94]	[233]
Ionotropic glutamate receptors (iGluRs)		
Native NMDA receptors	Rat cortical pyramidal neurons [132]	[132]
NR1/NR2A	Mainly CNS [46]	[137]
NR1/NR2B	Mainly CNS [46]	[137]
NR1/NR2C	Mainly CNS [46]	[137]
Native AMPA receptors	Rat CA1 pyramidal neurons [4]	[4]
Ca^{2+}-release channels		
$Ins(1,4,5)P_3$ receptor	Ubiquitous [58]	[65, 91, 127]
Ryanodine receptor (RyR1)	Skeletal muscle [165]	[98, 148]
Other channels		
Connexin Cx43	Widespread, dermal fibroblasts, glial cells, heart [104, 205]	[205]
Hair cell mechanotransduction channels	Frog saccular hair cells [81]	[81]
Volume-regulated anion channel (VRAC)	Widespread, epithelial cells [144]	[219]
Transporters and exchangers		
Plasma membrane Ca^{2+}-ATPase (PMCA1)	Ubiquitous [26]	[33, 56, 142]
Na^+/Ca^+ exchanger (NCX1)	Cardiac myocytes, neurons, skeletal muscle, smooth muscle, kidney [18]	[5, 73, 77, 78, 161, 207, 222]
Na^+/H^+ exchanger (NHE1)	Ubiquitous [147]	[1]
Na^+/HCO_3 cotransporter (NBCe1-A)	Renal proximal tubule, eye [174]	[215]

This table summarizes ion channels that have been shown to be sensitive to phosphoinositide modulation and can be categorized in the following groups: inwardly rectifying potassium (Kir) channels, two-pore potassium (K2P) channels, sodium (Na^+) channels, chloride (Cl^-) channels, P2X receptors, ionotropic glutamate receptors (iGluRs), calcium ($Ca2^+$)-release channels, and other channels. Transporters and exchangers that have been shown to be sensitive to phosphoinositides also appear in the corresponding group. The tissue distribution of each protein is provided on the second column, largely drawing from the IUPHAR database [70] but also from specific references that complement the database, as indicated. Specific references for the regulation of each channel/transporter by phosphoinositides are cited on the third column

Table 2

Phosphoinositide (PIP)-sensitive channels

Channel	Tissue distribution	References on PIP-sensitive channels
Kv channels		
Kv1.1/Kvβ1.1	Brain, heart, retina, skeletal muscle [70]	[149]
Kv1.3	(Human) T- and B-lymphocytes, alveolar macrophages, monocyte-derived macrophages, prostate epithelium, platelets, cerebral cortical grey matter, (rat) testis [70]	[135]
Kv1.4	(Human) brain, heart, pancreatic islet, (rat) skeletal muscle, arterial smooth muscle, retina [70]	[149]
Kv1.5/Kvβ1.3	(Rat) pulmonary arterial smooth muscle, spinal cord, brain, heart, (mouse) skeletal muscle, (human) pancreatic islet, atrial myocytes, atrium, ventricle [70]	[45]
Kv3.4	(Rat) parathyroid, prostate, brain, skeletal muscle, (mouse) pancreatic acinar cells [70]	[149]
Kv7.1 (KCNQ1)	(Human) heart=pancreas>kidney>lung=placenta, (mouse) intestine, stomach, liver, thymus [70]	[229]
Kv7.1 (KCNQ1)/KCNE1	Heart, inner ear [70, 123]	[123, 229]
Kv7.2 (KCNQ2)	(Human) brain (cortex and hippocampus), (rat) sympathetic ganglia, high expression levels in the cerebellum, cortex, and hippocampus [70]	[74, 75, 196, 229]
Kv7.3 (KCNQ3)	(Human) brain (cortex and hippocampus), (rat) sympathetic ganglia, lower expression levels in the cerebellum than in cortex and hippocampus [70]	[74, 75, 111]
Kv7.2/7.3 (KCNQ2/3)	Brain [70]	[57, 74, 111, 152, 170, 193, 196, 212, 224, 229]
Kv7.4 (KCNQ4)	Cochlea (outer hair cells), brainstem auditory nuclei [70]	[74, 75, 111, 229]
Kv7.5 (KCNQ5)	Brain, skeletal muscle [70]	[229]
Kv11.1 (HERG)	Heart, brain, gut, pancreatic beta cells, kidney, others [70]	[12, 13, 80]
CNG (cGMP-gated) channels		
Native rod CNG channel	Bovine rod outer segment [213]	[213]
Native olfactory CNG channel	Rat olfactory receptor neurons [227]	[227]
CNGA1	Retina, pineal gland, some neurons [70]	[213]
CNGA1/B1	Retina [70]	[213]
CNGA2	Olfactory neurons, hippocampus [70]	[20, 227]
CNGA2/CNGA4	Olfactory neurons [70]	[227]
CNGA3/CNGB3	Retina	[22]
Hyperpolarization-activated channels (HCN)		
HCN1	Brain, retina, sinoatrial node cells [70]	[154, 235]
HCN2	Brain, retina, heart [70]	[154, 155]
HCN4	Brain, retina, heart, testis [70]	[235]
K_{Ca} channels		
K_{Ca}1.1 (SLO1)	Ubiquitous, brain, skeletal muscle, smooth muscle, adrenal cortex, cochlear hair cells, pancreas, colon, kidney [211]	[204]
Ca_v channels		
Ca_v1.2 (L-type)	Heart, brain, prostate, bladder, uterus, stomach, colon, small intestine, placenta, adrenal gland, spinal cord [70]	[138, 234]

Channel	Tissue distribution	References on PIP-sensitive channels
$Ca_v2.1$ (P/Q-type)	Brain, heart, pancreas, pituitary [70]	[176, 214, 234]
$Ca_v2.2$ (N-type)	Brain, spinal cord [70]	[62, 106, 170, 214]
TRP channels		
TRPV1	Dorsal root ganglia, brain, kidney, pancreas, testes, uterus, spleen, stomach, small intestine, lung, liver [70]	[21, 36, 117, 126, 164, 192, 221]
TRPV1t (taste receptor variant)	Rat chorda tympani taste nerve [128]	[128]
TRPV5	Kidney, prostate, testes, placenta, pancreas, brain [70]	[107]
TRPV6	Intestines, stomach, placenta, salivary glands, liver, prostate, pancreas, kidney, testes, mammary glands [70]	[199, 200]
TRPM4	Small intestine, prostate, colon, kidney, testes, heart, lymphocytes, spleen, lung, brain, pituitary, skeletal muscle, stomach, adipose tissue, bone [70]	[145, 231]
TRPM5	Taste tissue, stomach, intestines, uterus, testis [70]	[115]
TRPM7	Ubiquitous, heart, pituitary, bone, adipose tissue [70]	[177]
TRPM8	(Rat) dorsal root ganglia, trigeminal ganglia, (human) prostate, testis, bladder>breast, thymus [70]	[21, 43, 116, 173, 206]
TRPA1	Brain, heart, small intestine, lung, skeletal muscle, and pancreas (mouse) dorsal root ganglia, trigeminal ganglia, nodose ganglia, nociceptive neurons, inner ear (organ of corti) [70]	[2, 42, 95]
TRPC1	Heart, brain, lung, liver>spleen, kidney, testis [70]	[179]
TRPC3	Pituitary gland>brain, heart, lung, dorsal root ganglia [70]	[109]
TRPC4	Heart, brain, pancreas, placenta, kidney [70]	[150]
TRPC5	(Mouse) brain, testis, kidney, uterus [70]	[203]
TRPC6	Heart, lung, kidney, muscle, intestine, stomach, pancreas, prostate, bone, brain [70]	[3, 87, 103, 109]
TRPC7	Kidney, intestine, pituitary gland, brain [70]	[109]
TRPC1/C5/C6	Rabbit coronary artery myocytes [180]	[180]

This table summarizes ion channels that have been shown to be sensitive to phosphoinositide modulation and can be categorized in the following groups: voltage-gated potassium (Kv) channels, cyclic nucleotide-gated (CNG) channels, hyperpolarization-activated (HCN) channels, calciumactivated potassium (K_{Ca}) channels, voltage-gated calcium (Ca_V) channels, and transient receptor potential (TRP) channels. The tissue distribution of each channel is provided on the second column, drawing from the IUPHAR database [70] and from specific references complementing the database, as indicated. The tissue distribution shown for Kv1.1/Kvβ1.1 and Kv1.5/Kvβ1.3 heteromers pertains to Kv1.1 and Kv1.5, respectively. Specific references for the regulation of each channel by phosphoinositides are cited on the third column