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Review

Membrane channels as integrators of G-protein-mediated signaling☆,☆☆

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ABSTRACT

A variety of extracellular stimuli regulate cellular responses via membrane receptors. A well-known group of seven-transmembrane domain-containing proteins referred to as G protein-coupled receptors, directly couple with the intracellular GTP-binding proteins (G proteins) across cell membranes and trigger various cellular responses by regulating the activity of several enzymes as well as ion channels. Many specific populations of ion channels are directly controlled by G proteins; however, indirect modulation of some channels by G protein-dependent phosphorylation events and lipid metabolism is also observed. G protein-mediated diverse modifications affect the ion channel activities and spatio-temporally regulate membrane potentials as well as of intracellular Ca^{2+} concentrations in both excitatory and non-excitatory cells. This article is part of a Special Issue entitled: Reciprocal influences between cell cytoskeleton and membrane channels, receptors and transporters. Guest Editor: Jean Claude Hervé.

Contents

1. Introduction

Ion channels are pore-forming proteins integrated in the cell membranes of all cells. The channels allow the movement of specific populations of ions across cell membranes, based on the electrochemical ion gradients between the inside and outside of the cell. Thus, the activity of channels is closely linked to the membrane potential, and extra- and intracellular ion concentrations. The pore of the channel proteins gates to restrict the permeation of ions and the gate of the pore is controlled by various stimuli. The ion channels consist of structurally and

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functionally distinct domains (Fig. 1): the transmembrane domain, which determines the selective permeation of ions by activation gate, and the regulatory domain, which transduces information from various stimuli and regulates the gate. Thus, the coupling of transmembrane and regulatory domains is crucial for the regulation of channel activity. Broadly, the ion channels are classified as voltage- and ligand-gated channels. The voltage-gated channels possess a membrane-integrated domain as a regulatory domain which senses the difference in the electrical potential across the membrane, while the ligand-gated channels possess a hydrophilic extra-membrane domain at the outside of the membrane, the domain of which directly associates with physical entities such as small chemicals and regulatory proteins.

The extracellular ligands regulate the ion channel activity by various mechanisms; at least 2 distinct mechanisms have been reported. The first mechanism is observed in ionotropic neurotransmitter receptors, where the ligands associate with the ligand-binding domain located at the extracellular side. Upon specific ligand binding, a conformational shift to the open active state occurs. This response is fast, occurs within milliseconds, and is short-lived (<0.1 s). The second mechanism underlies the functioning of metabotropic receptors having hepta-helical domains: the G protein-coupled receptors (GPCRs). In this case, the ligand binding stimulates G protein signaling, and consequently modulates the channel activity. This response is relatively slow, occurring within a second, but is long-lived and can last from minutes to hours.

G proteins are anchored to the inner leaflet of the cell membranes by covalently attached fatty acid chains [1–3]. This characteristic feature of G-proteins allows them to signal and modulate the channel activity from the cytoplasmic side. The direct or indirect action of G-proteins on the ligand-binding domain of channel proteins shifts their conformational equilibrium. This in turn facilitates the structural transition of the allosterically coupled transmembrane domain, regulating the activation gate of the channels.

2. Overview of G proteins, their coupled receptors, and regulators of G protein signaling

The GPCRs constitute the largest family of membrane-embedded proteins encoded by the mammalian genome [4,5]. The GPCRs possess an extracellular N-terminus and an intracellular C-terminus (Fig. 2). G proteins constitute 3 major subunits Gα, Gβ, and Gγ [1,3]. Gα binds a guanine nucleotide and hydrolyzes GTP to GDP. Under physiological conditions, the Gβ and Gγ associate tightly to form a dimer (Gβγ) by a coiled-coil interaction. Gα has been classified into four groups ($G\alpha_s$, $G\alpha_i$, $G\alpha_q$ and $G\alpha_{12}$) based on sequence similarity, coupling effectors, and sensitivity to bacterial ADP-ribosylating exotoxins [1–3]. Although the location of the ligand-binding site varies among the GPCRs, they may show similar conformational changes such as the rearrangement of transmembrane helices, the generation of a crevice at the intracellular surface of the receptor, and the accommodation of the C-terminus of Gα at the cytoplasmic interface, to accomplish G protein activation (Fig. 2) [2,6]. However, the presence of multiple points of contact between the GPCR, and Gα as well as Gβγ has been proposed to determine the specificity of the GPCR–G protein interaction [7].

The Gα exists in an inactive GDP-bound state (Gα–GDP), which exhibits a high affinity for Gβγ [1,3]. Ligand binding to GPCRs forces the release of GDP from Gα, and Gα is now allowed to GTP binding. GTP-bound Gα (Gα-GTP) has a lower affinity towards Gβγ, and eventually dissociates from Gβγ. Thus, the independent components of G proteins (Gα-GTP and Gβγ) further transduce signals to their downstream effectors. G protein signaling is terminated by the hydrolysis of the bound GTP to GDP, followed by the association of resultant Gα-GDP with Gβγ. If the GPCR is still bound to the agonist, the cyclic reaction is restarted by dissociation of the bound GDP from the Gα subunit.

The regulator of G protein signaling (RGS) protein was initially identified as a negative modulator of the G protein signaling in the nematode *Caenorhabditis elegans* [8]. This finding led to the identification of a gene family consisting of more than 30 members, which share a conserved 120 amino-acid stretch called RGS domain [8–10]. The RGS domain binds to Gαs in a subtype-specific manner and accelerates their intrinsic GTP hydrolysis [11]. The N- and C-termini of the RGS proteins are variable in sequence and occasionally possess protein-binding motifs [9,10,12,13]. Furthermore, several RGS proteins contain palmitoylation site(s), and the introduction of a mutation at this site resulted in the mistargeting of cholesterol-rich membrane lipid rafts [14] and changes in RGS activity [15–18]. These structural features enable the RGS proteins to function as spatio-temporal regulators of G protein signaling. Their effects on ion channels will be discussed in more detail later on in this review.

3. The indirect action of G proteins on ion channels

One of the best-understood G protein-mediated modulations of ion channel activity involves sympathetic stimulation in the heart (Fig. 2). Noradrenaline released from the nerve termini activates G_s by binding to the β_1-adrenergic receptor (β_1AR) and augments adenylyl cyclase (AC) activity, which converts ATP to cyclic AMP (cAMP) [19]. cAMP directly associates with and activates the pore-forming cyclic nucleotide-gated non-selective cation channel subunit, resulting in increase in the pacemaker current in cardiac nodal cells [20]. Therefore, the activation of these channels shortens the interval of action potentials, leading to an increased heartbeat. On the other hand, in cardiac myocytes, cAMP binds to the regulatory subunits of cAMP-dependent protein kinase (PKA) and activates its catalytic subunit. PKA phosphorylates cardiac

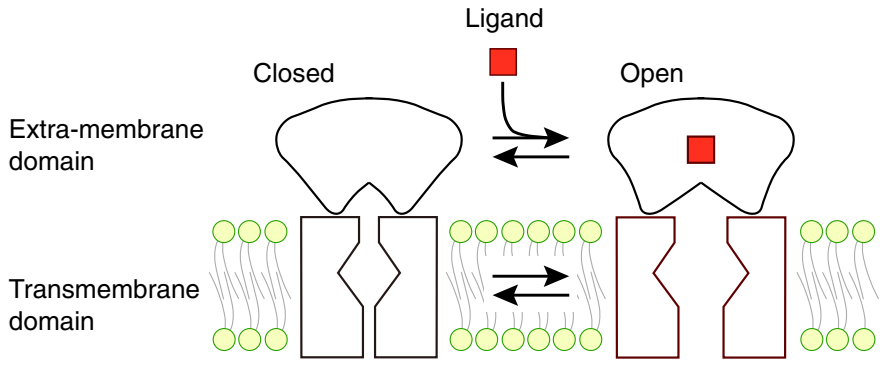

Fig. 1. Schematic representation of ligand-induced conformational changes in the regulation of ligand-gated ion channels. The ligand-gated ion channels consist of 2 distinct domains: the transmembrane domain and extra-membrane domain. Each domain may exist in at least 2 physiologically distinct conformations supporting the inactive (closed) and active (open) states of the channels. The ligand binding to the domain located at the outside of membranes shifts the conformational equilibrium toward the open state. The shift influences the conformational equilibrium of the allosterically coupled transmembrane domain, leading to the opening of the channel.

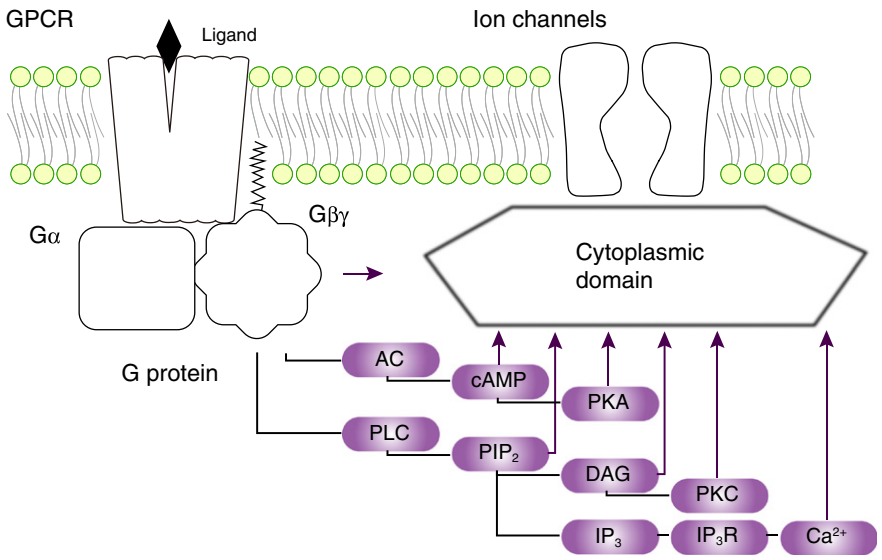

Fig. 2. Modulation of membrane channel activity by G protein-mediated signaling pathways. Extracellular ligands (diamond) associate with G protein-coupled hepta-helical receptor (GPCR) and activate G proteins. Dissociated GTP-bound Gα and Gβγ subunits regulate the activity of intracellular downstream effectors. The changes in the concentrations of metabolites and functional state of the effectors diversely modulate the channel activity. On the other hand, some of the ion channels are under the direct control of either Gα or Gβγ. Abbreviations: AC = adenylyl cyclase, cAMP = cyclic AMP, PKA = protein kinase A, PLC = phospholipase C, DAG = diacylglycerol, PKC = protein kinase C, IP_3 = inositol 1,4,5-trisphosphate, IP_3R = IP_3 receptor.

L-type Ca^{2+} channels and further enhances the current amplitude [21–24]. This pathway can contribute to the regulation of excitation–contraction coupling [25,26]. Furthermore, the β_1AR/G_s/AC/PKA pathway shortens the duration of the action potential and decreases the refractory period [27]. This phenomenon is based on the PKA-dependent phosphorylation of the pore-forming subunit (KCNQ1) of the I_{Ks} (slowly activating delayed rectifier K^+ current), leading to the augmentation of the I_{Ks} density [28,29]. In addition, the increased Ca^{2+} influx through phosphorylated L-type Ca^{2+} channels accelerates the Ca^{2+}-dependent inhibition of the channel, contributing to earlier repolarization [30,31].

Since the ion channel is embedded within the cell membranes, lipids are intrinsically involved in the regulation of channel activity. Phosphatidylinositol-4, 5-bisphosphate (PIP_2) is an essential phospholipid involved in the maintenance of channel activity [32]. The level of PIP_2 in the membranes is maintained by a balance between hydrolytic activity of phospholipase C (PLC) and the synthesis by PI kinase [33]. The PLC is a downstream target of G_q-coupled GPCR. An example of this type of regulation is the M-current in neurons such as superior cervical sympathetic ganglion neurons [33], dopaminergic neurons [34], and pyramidal tract neurons [35]. The current is robustly suppressed by acetylcholine (ACh) via m_1- and m_3-muscarinic receptors, leading to an increase in the firing rate of neurons [36]. Since pore-forming KCNQ subunits of the M-current require the direct association of PIP_2 for their activity, the depletion of PIP_2 pool by the GPCR-stimulation strongly shuts down the M-current [37–39]. Further, PIP_2 involves the regulation of various ion channels such as the inward rectifier K^+ (Kir) channels [40–42], the background two-pore domain K^+ (K2P) channels [43], and the transient receptor potential (TRP) channels [44–47].

PLC activation leads to the cleavage of PIP_2 into inositol 1, 4, 5-trisphosphate (IP_3) [48] and diacylglycerol (DAG) [50]. The former triggers the release of Ca^{2+} from intracellular pools and the latter activates protein kinase C (PKC) [51]. An increase in intracellular Ca^{2+} activates the Ca^{2+}-dependent K^+ [52,53], and Cl^- channels [54,55], and modulates the voltage-dependent Ca^{2+} channels [56,57]. PKC activation leads to increased phosphorylation of downstream target channels. Interestingly, the PKC-mediated phosphorylation inhibits the activity of the canonical TRP (TRPC) channel subfamily, while DAG directly activates this family of channel proteins [58]. In smooth muscles, ACh stimulation activates TRPC channels (TRPC1, TRPC3, TRPC4, TRPC5 and TRPC6) by removal of inhibitory action of PIP_2 [59,60] and the direct association of G proteins as discussed below. Therefore, G_q-coupled signaling regulates this vasoactive receptor-operated Ca^{2+} entry diversely [61–64].

The cAMP cascade is also important for the regulation of subcellular localization of ion channels. G protein-gated Kir channels in thyrotroph cells of the anterior pituitary lobe localize on the membranes of intracellular dense core vesicles, which contain thyrotropin [65]. But the channels are recruited to the plasma membrane upon stimulation by thyrotropin-releasing hormone and stimulated by extracellular dopamine and somatostatin [65]. The aquaporin water channel, AQP2 is predominantly present in intracellular vesicles of collecting duct cells in the kidney, but vasopressin enhances the trafficking of AQP2 to the apical membrane via vasopressin V_{1A} receptor–G_s–AC–PKA pathway [66,67].

The studies on the phosphorylation-dependent modulation of various ion channels raise the question about how the signaling specifically propagates to the targets. The key mechanism underlying this modulation is the localization of signaling molecules by scaffolding proteins, such as A-kinase anchoring proteins (AKAPs) [68]. In cardiac myocytes, Yotiao/AKAP9 recruits the PKA, protein phosphatase 1 and type 9 AC, and binds to the cytoplasmic domain of KCNQ1 [28,69,70]. The formation of protein complex is essential for the regulation of I_{Ks} by the sympathetic nerve. Furthermore, the binding of AKAP79/150 to KCNQ2 facilitates receptor-dependent suppression of M-current [71,72]. In smooth muscle, large-conductance voltage- and Ca^{2+}-activated K^+ channels have been shown to assemble with β_2-adrenergic receptor, AKAP79/150, PKA, and L-type Ca^{2+} channels [73,74]. The AKAPs are not the only group of proteins involved in clustering of G protein signaling molecules. The signaling molecules themselves have been reported to preferentially localize within close proximity to the plasma membrane. Thus, diverse G protein-mediated signal pathways modulate ion channel activity at multiple levels.

4. Direct interaction of G protein with ion channels

Thus far, we have discussed diverse G protein signal pathways that indirectly modulate the activity of membrane channels. However, it is well known that the direct interaction of G proteins also plays an

essential role in the physiological regulation of the ion channels. In neurons, various inhibitory neurotransmitters such as dopamine, noradrenarine, serotonin, and neuropeptide Y attenuate the activity of the voltage-dependent P/Q-type and N-type Ca^{2+} channels at the presynaptic nerve termini [75–80]. Reconstitution experiments using heterologous expression systems have revealed that Gβγ interacts with a pore-forming α subunit of Ca^{2+} channels in a membrane-delimited pathway [81–83]. Likewise, intracellular inhibition of pathway components was accounted for by slowing the activation kinetics, and shifting the voltage-dependency of activation gating in the positive direction [76,84,85]. It has been proposed that Gβγ associates with the α subunit of the channels through its N-terminus [86–89], the I–II linker [90,91], and the C-terminus [92,93]. However, the contribution of these regions for the association with Gβγ is debatable and depends on whether they are positioned at the direct binding site or play auxiliary roles such as supporting the formation of the binding pocket and the transmission of the Gβγ-evoked conformational changes within the channel. The cytoplasmic β subunit of Ca^{2+} channels has been recognized to be important for Gβγ-dependent modulation [94–101]. However, the precise mechanism of the ternary interaction has yet to be investigated [102].

TRP channels are a family of cation channels under the control of multimodal stimuli [44–47], and G-protein signaling take part in their regulation *in vivo*. In the dark, the photoreceptor cells release glutamate, which binds to mGluR6 and attenuates the activity of a non-selective cation channel TRPM1 via G_o protein [103–105]. Gβ3 is crucial for this signaling [106], and Gβγ has been proposed to mediate the mGluR6-dependent closure of TRPM1 [107]. The TRPM1-deficient mice lack a b-wave in the electroretinogram [104], and mutations of this channel protein in humans lead to night blindness [108–110].

It is evident that the 'leak' two-pore domain K^+ (K2P) channels contribute to the maintenance of the resting membrane potential in various types of excitable and non-excitable cells [111–113]. The activity of these K2P channels is regulated by diversified stimuli. PIP_2 is one of intracellular molecules important for the activation of K2P channels such as TASK1, TASK3, TREK1 and TRAAK [43]. Recently, Woo et al. found that protease-activated GPCR stimulation evokes the fast and slow release of glutamate from astrocytes [114]. They presented that astroglial K2P channel TREK1 is the molecular entity mediating fast response, and the direct association of free Gβγ with its N-terminus triggers the activation of the channel.

Glycine-activated ion channels regulate the excitability of the mammalian brain stem and spinal cord. Both GPCR stimulation and application of purified Gβγ enhance the glycine receptor activity by increasing its probability of the channel being open (P_o) [115]. As mentioned previously, TPPC channels are regulated by G_q-signaling pathways and by $G\alpha_i$ itself [116]. Therefore, various types of ion channels have been reported to be under the direct control of G proteins. In the following sections, we will discuss in detail about G protein-gated Kir channels as an extensive example for direct modulation of ion channels by G proteins.

5. Direct G protein interaction with Kir channels

5.1. Historical background of G protein-dependent regulation of Kir channels

In the heart, ACh released from vagal nerve termini reduces the heart rate and slows the atrioventricular conduction [117,118]. ACh hyperpolarizes the membrane potential by increasing K^+ efflux (I_{KACh}) [119–121]. The manner of K^+ conduction in I_{KACh} is unique constituting a large inward K^+ current regarding membrane potential (V_m) negative relative to the equilibrium potential of K^+ (E_K), and a less outward current at V_ms positive relative to E_K [121,122]. Based on this characteristic conduction property, the channels encoding I_{KACh} have been classified as members of a family called "inward rectifier" K^+ (Kir) channels. The I_{KACh} activation by m_2-muscarinic receptor is mediated by pertussis toxin-sensitive G proteins [123–126]. G protein-gated Kir channels are also responsible for the formation of slow inhibitory postsynaptic potentials in the central nervous system [127,128]. A variety of $G_{i/o}$-coupled GPCRs have been reported to regulate the Kir channel activity [129,130].

5.2. Subunit composition of G protein-gated Kir channels

G protein-gated Kir channels (Kir3.1–Kir3.4) belong to the Kir channel family [127,129,131]. A growing number of microbial genome sequences indicate that prokaryotes occasionally possess genes encoding Kir channels [132]. Four individual subunits within the same subgroup of Kir channels assemble to form homo- or heteromeric units [129,130,133,134]. I_{KACh} comprises of Kir3.1 and Kir3.4 [135,136]. Meanwhile, the neuronal G protein-gated Kir channels are either homomeric assemblies of Kir3.2 [137,138] or heteromeric assemblies of Kir3.1, Kir3.2, and Kir3.3 [137–144]. These observations were confirmed by the lack of Kir-related physiological responses in mice following disruption of Kir channel genes [145–150].

5.3. Kir channel structure

The Kir channels consist of 4 subunits; each subunit contributes to the formation of the transmembrane domain and cytoplasmic domain (Fig. 3A) [151,152]. Each domain of the Kir channel exhibits a 4-fold symmetry axis where an ion conduction pathway is located, and the N- and C-termini exposed to the cytoplasm, assemble to form the cytoplasmic domain. The cytoplasmic termini sandwich the transmembrane domain, which possesses 2 short α helixes (an amphiphilic slide helix and a pore helix that points to the ion conduction pathway), and 2 membrane-spanning M1 and M2 helixes [153]. The M2 helix forms a hydrophobic barrier and forces a constraint on a continuous water-filled pore for regulating ion diffusion; this structural element, therefore, functions as an activation gate [152,154,155]. Except for the slide helix, the proposed arrangement of these structural elements in the transmembrane domain of Kir channels is similar to that observed in other K^+ channels such as the bacterial pH-gated KcsA channel [156], bacterial Ca^{2+}-activated MthK channel [154,157], bacterial voltage-gated KvAP channels [158], mammalian voltage-gated Shaker K^+ channel [159,160], and mammalian K2P channels [161] as well as the bacterial voltage-gated Na^+ channel [162], mammalian ionotropic glutamate receptor [163], and bacterial non-selective cation NaK channel [164–166]. Furthermore, the substitution of the transmembrane domain of Shaker and Kir2.1 with KcsA yields chimeric K^+ channels that are functionally similar to the original ones [167]. Therefore, the structural rearrangement in the transmembrane domain of K^+ channels is thought to be similar between ligand- and voltage-gated K^+ channels, and the conformational transition of the transmembrane domain is the target of the cytoplasmic domain of Kir channels [168].

The cytoplasmic domain comprises 3 β sheets and has an immunoglobulin-like fold (Fig. 3A) [151,152]. The cytoplasmic N-terminus forms a β sheet with the C-terminus, and connects to the slide helix of the transmembrane domain (Fig. 3B). Thus, the subunit interface comprises both the N- and C-termini. At the center of the subunit assembly, there is an ion-conduction pathway that can extend across the length of the transmembrane domain. The amino acids in the internal surface of the cytoplasmic pore can affect the inward rectification property [151,169,170]. Therefore, the cytoplasmic pore permits the traversing of inorganic ions such as K^+ and Mg^{2+} [171,172], organic molecules such as polyamines [169,170,173], and pore blockers [174–176].

5.4. Functional states underlying Kir channel activity

The opening and closing of the conduction pathway is directly coupled to the activity of the Kir channel [177–180]. The macroscopic

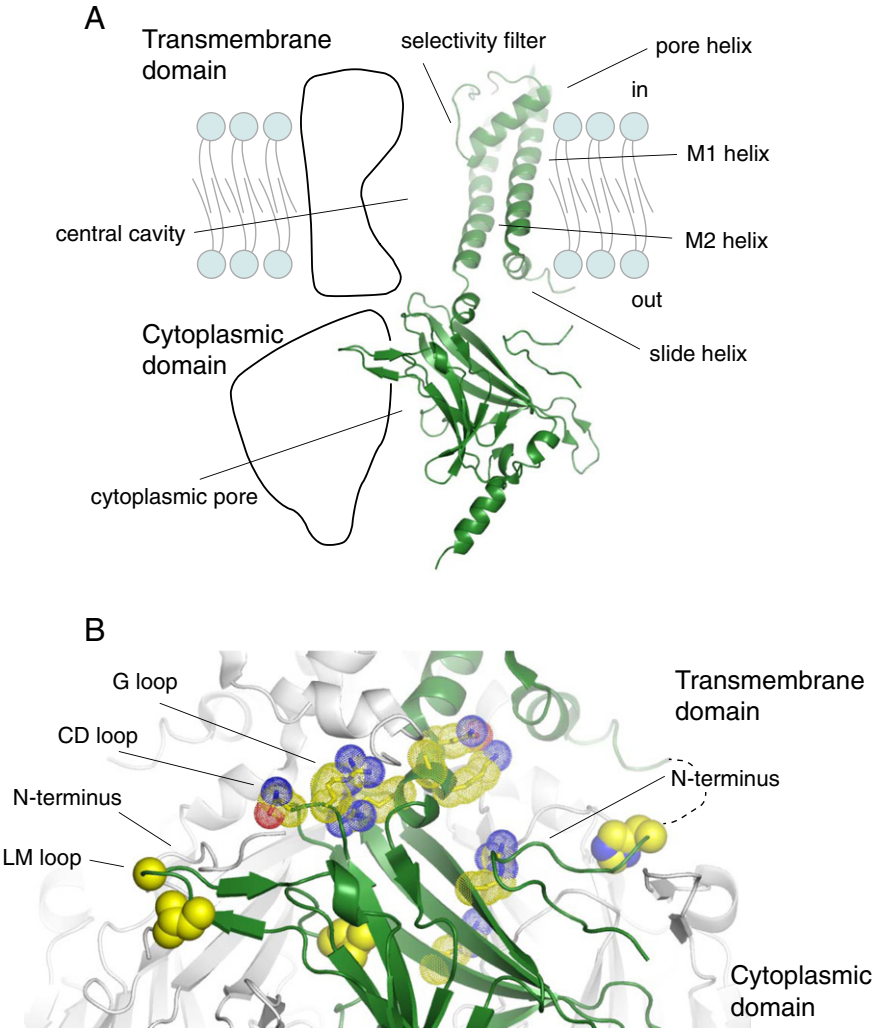

Fig. 3. Structural features of G protein-gated Kir channels. (A) Molecular architecture of G protein-gated Kir channels. The ion conduction pathway is present at the center of a tetrameric subunit assembly. The side view of Kir3.2 crystal structure (PDB ID: 3SYO) is arranged with a cartoon of the channel [222]. The channel consists of the transmembrane and cytoplasmic domains. Structural elements crucial for the channel function are also shown. (B) Distribution of amino acids important for the channel activation. The side view at the interface between 2 domains is shown for the Kir3.2 amino acids (His69, Leu273, Leu344, and Gly347) that may be crucial for Gβγ-dependent activation (spheres). The amino acids (Gln197, Lys199, Lys200, Arg201, Arg230, Asn231, Arg240, and Arg324) of Kir3.2, which correspond to the residues crucial for PIP_2-dependent activation in other Kir channels, are shown by dots. A dashed line indicates a missing loop between the 2 domains.

current amplitude generated by Kir channels can be defined by the number of channels in the patch membrane, the P_o and the single-channel conductance (γ). The γ of either a native or recombinant G protein-gated Kir channel is dependent on the difference between V_m and E_k, and is independent of receptor stimulation [181–185]. An increase in the P_o of the channels often correlates with the increase in current amplitude caused by Gβγ. The histogram of the single-channel conductance of Kir channels exhibits a single Gaussian distribution, strongly suggesting that Kir channels have a single open-pore configuration [186,187]. Furthermore, the histogram of the single-channel dwell time in the open state can be fit by a single exponential curve, implying that the channel has a single open state. On the other hand, the histogram of single-channel dwell time in the closed state reveals that there are at least 2 non-conductive states. Therefore, it seems likely that the activity of Kir channels can be functionally defined by the equilibriums between a single open conformation and multiple closed conformations.

However, analyses of G protein-gated Kir channels from cells isolated by enzymatic digestion of tissues suggested that they exhibit bursting behavior upon Gβγ association, and their activation is based on a shift between different gating modes, which are characterized by the frequency of channel opening and mean open time of the channel [182,184,185,188]. Furthermore, the channels have at least 2 open states, and Gβγ binding prolongs its mean open time duration, which is inversely coupled to the duration of the subsequent closed intervals [183]. Since the opening of the channel pores is dependent on PIP_2 [189–192], the difference in the channel kinetics could be accounted for by the variation in the plasma membrane PIP_2 content. Although the channels exist in different modes, they share the same single channel conductance. Therefore, the correlation observed between the conductive open conformation and the open state of the channels, which is predicted by single channel kinetic analysis, remains elusive.

5.5. Gβγ: a physiological activator of G protein-gated Kir channels

Perfusion of the intracellular side of the inside-out patch membranes with non-hydrolysable GTP analogs and purified Gβγ resulted in the activation of the native I_{KACh} [193–198]. When Kir3.1 is exogenously expressed in *Xenopus* oocytes, the reconstituted channel is activated either by the stimulation of co-expressed m_2R [199] or the co-expression of Gβγ [200]. Co-expression of Gβγ-binding protein [200] or introduction of Gβγ mutations disrupted the Gβγ-mediated channel activation

[201,202], validating that Gβγ mediates GPCR-dependent channel activation.

Gβγ is predominantly anchored to the cell membranes by post-translational isoprenylation at the C-terminus of the Gγ subunit [1–3]. Many studies had focused on the association of Gβγ with the cytoplasmic domain of G protein-gated Kir channels. Initially, the cytoplasmic C-terminus of Kir3.1 or both the N- and C-termini of Kir3.x (Kir3.1–Kir3.4) were found to associate directly with Gβγ [203–205]. The residues of Kir3.x subunits that are required for its association with Gβγ have been identified [206–208], and include His69, Leu273, Leu344, and Gly347 in Kir3.2; His69 is located at the N-terminus, Leu344 and Gly347 are positioned on a loop between the βL and βM strands, and Leu273 is in the protein core (Fig. 3B). Yokogawa et al. performed nuclear magnetic resonance analysis and reported that the residues that associate with Gβγ span the molecular surface of 2 neighboring subunits in the tetrameric assembly of the cytoplasmic domain of Kir3.1 [209]. They also show that the residues displaced upon the association of Gβγ are distributed not only around the Gβγ-binding site, but also at the subunit interface and a membrane-facing loop between the βH and βI strands (G loop). Based on the crystal structure of Kir3.2 and Gβγ complex, these residues are confirmed to be involved in the Gβγ recognition [40,191,210]. These findings suggest that Gβγ binding causes substantial changes in the conformation of the cytoplasmic domain, leading to the channel opening.

5.6. Phosphoinositide: a lipid essential for Kir channel activation

Gβγ is a physiological activator of G protein-gated Kir channels, but requires other factors to activate these channels. All Kir channels require the binding of PIP_2 for their activation [32,192,211,212], and therefore, the lipid is also a prerequisite for the opening of G protein-gated Kir channels [40,191,210]. The Gβγ association may play a role in strengthening the channel-PIP_2 interactions [32,189,191,192,210,213,214]. Differences in the turnover rate of PIP_2, the membrane properties conferred by lateral diffusion of PIP_2, and the association of signaling components with the lipid rafts may determine the variation in the PIP_2-sensitivity of G protein-gated Kir channels across cell types [215–218]. Many residues are involved in PIP_2 binding, and these are distributed throughout the tertiary structure of the channel (Fig. 3B) [219]. The interface between the transmembrane domain and cytoplasmic domain, namely the core region, can be divided into 3 regions: the N terminus [192], a cationic amino acid cluster proximal to the M2 helix [189,192,211,212,220,221], and a loop between the βC and βD strands (CD loop) [42,213]. Crystallographic analyses of Kir3.2 indicate that PIP_2 lies adjacent to the M2 helix and interacts with a cluster of positively charged residues at the linker region between the transmembrane domain and cytoplasmic domain [222]. A subset of inherited mutations in Kir channels located at the linker lowers the Kir channel sensitivity to PIP_2 binding and has been implicated in malfunctioning of various tissues [192]. Intriguingly, this mode of binding is observed when the channel is not only in a closed state [222,223], but also in an open state [222]. Therefore, the role of PIP_2 in the regulation of the activation gate at the transmembrane domain and the mechanism by which the lipids drive the channel to an open state remain unclear.

5.7. Gα and RGS proteins: roles in regulation of channel function and the clustering of signaling molecules

It becomes apparent that Gα of the PTX-sensitive G protein also modulate the G protein-gated Kir channels [224–227]. Gα affects the basal activity and the activation kinetics of the channel. The mode of binding and the modulation of the gating kinetics are dependent on the individual Gαs [225,228]. Gα interacts with the channel with a lower affinity than Gβγ and exhibits non-competitive binding kinetics when compared to Gβγ. On the other hand, it has been proposed that the heterotrimeric G proteins couple with the channels prior to GPCR-mediated activation and the subsequent rearrangement of subunits and their binding modes lead to the activation of channel proteins [229]. The exact stereochemistry of the association of Gα–Gβγ complex with the channel and the mechanism by which the nucleotide-bound states of Gα affects the mode of binding has yet to be understood [227,228,230]. However, the pre-coupled assembly of G protein subunits with the channel suggests that the cytoplasmic domain of G protein-gated Kir channels functions as a scaffolding module to determine the timing of G protein signaling.

The heterologous expression of RGS proteins with GPCR and G protein-gated Kir channels using *Xenopus* oocytes or mammalian cell lines resulted in the reconstitution of rapid turn-on and turn-off responses during GPCR stimulation [49,231–233]. RGS proteins also modulate the voltage-dependent 'relaxation' of the inward current of the I_{KACh} [234]. These effects of the RGS proteins are mediated by the RGS domains conserved among the family members [235]. The acceleration of the turn-on response of the I_{KACh} by the RGS proteins suggested their close proximity within the cell. To understand the geometrical arrangement of these signaling components, fluorescent proteins were tagged to 2 of the components simultaneously and Förster resonance energy transfer (FRET) was measured to estimate their distance in cells expressing these proteins exogenously. These studies reported detectable FRET signals between these proteins [236–246], suggesting that GPCRs, G proteins and RGS proteins as well as G protein-gated Kir channels are present in close proximity. Pacemaker cells isolated from the sinoatrial nodes of transgenic mice lacking either RGS4 [247] or RGS6 [248] exhibited enhanced sensitivity to a carbachol-mediated reduction of spontaneous action potential firing. These mice increased negative chronotropic responses to carbachol. Thus, the RGS proteins physiologically regulate parasympathetic activation in the heart. Furthermore, γ-aminobutyric acid (GABA)-induced K^+ currents in the hippocampal CA1 neurons of RGS7-null mice are characteristically similar to those of the channels reconstituted in the absence of RGS proteins [245]. It was also reported that a delay in the activation and deactivation kinetics of metabotropic GABA receptor agonist-evoked inward K^+ currents was observed in the cerebellar granule cells of RGS6-null mice [249]. This indicates that the RGS proteins play a critical role in controlling G protein-mediated ion channel activity *in vivo*. In addition, these reports suggest that not only the ion channels, but also GPCRs act as scaffold signaling molecules for the integration, specificity, and fine-modulation of G protein-mediated signaling.

5.8. Structural elements responsible for gating

At present, various structural analyses of Kir channels suggest several macroscopic conformational changes of the cytoplasmic domain: a rigid-body movement against the transmembrane domain [223,229,250–253,254], a reorientation of subunits between the latched and unlatched states [252], and an expansion of the inner diameter of the cytoplasmic pore [255–261]. The first rigid-body movement could be separated into 2 different conformational changes: the change in distance between domains [223,250,251] and the rotation (clockwise and counterclockwise) [223,252,253,254]. The most recent crystal structure of the complex of mouse Kir3.2 and Gβγ indicates that Gβγ binds at the interfaces between 2 subunits [254]. The complex showed that the cytoplasmic domain is rotated about 4° anticlockwise relative to the transmembrane domain. Although the inner helices are partially splayed, the bundle-crossing region is still closed in the structure, and therefore, the authors suggest that the conformation of the complex that associates with Kir3.2 in the pre-open state and the unique binding causes the rotation of the cytoplasmic domain. This rotational motion may trigger the expansion of inner diameter of the cytoplasmic pore [255–261]. Since the pore in the closed state binds cations in the valency-dependent manner [257], a reduction in potential is required for K^+ diffusion through the pore.

In ligand-gated ion channels such as ionotropic glutamate receptors [163,262] and Ca^{2+}-activated K^+ channels [157,263,264], a ligand-induced conformational change at the ligand-binding domain is thought to mechanically force the opening of the activation gates in their transmembrane domains. At the top of the cytoplasmic pore, the G loop interacts with the transmembrane domain [222,253]. The loop is expected to mediate a tension in the cytoplasmic domain that drives the M2 helix of the transmembrane domain [209,253,261]. However, the G loop is positioned differently in various crystal structures [151,250,251,265,266], implying that the loop is structurally flexible. This feature permits the loop to occupy the top of the cytoplasmic pore in some crystal structures [250,251]. Therefore, the G loop is currently speculated to act as a cytoplasmic gate [222,250,251]. A change in the conformation of the G loop would be linked to the movement of the adjacent CD loop, which enables the G loop to shift its position greatly in crystal structures [151,222,251,267]. The constraint on the movement of the CD loop prevents the activation of the channel [268,269]. Furthermore, the binding of PIP_2 is simulated, leading to the stabilization of the CD loop and the alteration in position of the G loop [270]. As mentioned above, many residues in the cytoplasmic domain contribute to either PIP_2-dependent conformational changes or PIP_2 recognition. Experimental evidence along these lines implies that various structural elements in the cytoplasmic domain are displaced during the transition between open and closed states. Therefore, although the G loop is a candidate to mediate allosteric coupling between two domains, it is unclear how the channel transit from the closed to open state through multiple conformational steps to control the Kir channel activity.

6. Conclusion

The activity of ion channels is extensively regulated by G protein-mediated signaling. The intracellular surface of ion channels facilitates the direct interaction with G proteins and an indirect modulation by G protein-coupled signaling pathways. The G protein-dependent conditioning influences the conformational transition of the channels between the closed resting state and the open active state. This clearly suggests that the ion channel significantly changes its conformation at the intracellular ligand-binding domain or the cytoplasm-facing regions during opening and closing of the gate. Recent crystallographic analyses have convincingly clarified the configuration of the channel as the machinery for selective ion permeation. However, the study of static crystal structures has limited utility in elucidating various aspects of the structure–function relationship. Therefore, compared to what is known about G protein signaling based on physiological and biochemical analyses, the structural insights into G protein-mediated signaling and regulation of channels remain largely unclear. A comparison of large numbers of crystal structures or the improvement of specific methods for obtaining structural information on G proteins and channel proteins, or development of procedures that would not depend on crystallographic analyses might help address the questions on the structure–function relationships of these protein complexes.

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