

Regulation of TRP Channels by Phosphorylation

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Key Words

TRP channels · Phosphorylation · Ca²⁺ influx

Abstract

The transient receptor potential (TRP) channels are a group of Ca²⁺-permeable cation channels (except TRPM4 and TRPM5) that function as cellular sensors of various internal and external stimuli. Most of these channels are expressed in the nervous system and they play a key role in sensory physiology. They may respond to temperature, pressure, inflammatory agents, pain, osmolarity, taste and many other stimuli. Recent development indicates that the activity of these channels is regulated by protein phosphorylation and dephosphorylation of serine, threonine, and tyrosine residues. In this review, we present a comprehensive summary of the literature regarding the TRP channel regulation by different protein kinases.

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Introduction

Transient receptor potential (TRP) channels were first cloned in *Drosophila melanogaster*. Tremendous advances in recent years have resulted in the isolation of approximately 30 unique TRP homologs [1, 2]. These homologs have been divided into seven subfamilies: canonical TRPC, vanilloid TRPV, melastatin TRPM, poly-

cystin TRPP, mucolipin TRPML, ankyrin transmembrane proteins (TRPA) and NOMPC-like TRPN [1, 2]. TRP channels are Ca²⁺-permeable (except for TRPM4 and TRPM5) cation channels composed of four subunits. With the exception of some polycystins, all TRP subunits possess six transmembrane segments. TRPC, TRPV, and TRPA channels contain ankyrin repeats at their N-terminal cytoplasmic domains. These ankyrin repeats are thought to play key roles in protein-protein interactions [1, 3]. In addition, TRPC and TRPM both contain proline-rich domains in the region just C-terminal to the sixth transmembrane segment.

The importance of TRP channels in the nervous systems has been well documented [2, 4]. TRP channels serve as sensors to perceive and respond to environmental stimuli including temperature, taste, mechanical forces, pain and pheromones [2, 4], and then transform various environmental stimuli into changes in cytosolic Ca²⁺ levels and/or membrane potentials in peripheral neurons. In the central nervous system, TRP channels may underlie metabotropic glutamate receptor (mGluR)-mediated excitatory postsynaptic potentials (EPSPs) [5, 6]. Recent evidence indicates that TRP channels are crucial for the guidance of nerve growth cones in the developing nervous system [7, 8].

There is a high degree of diversity in the modes of activation and regulation of TRP channels. Physical (e.g., temperature and mechanical forces) and chemical (e.g., hormones, neurotransmitters and growth factors) stimuli activate different TRP channels via diverse mechanisms

including alteration of cellular diacylglycerol (DAG) levels, changes in cytosolic Ca^{2+} levels, depletion of Ca^{2+} stores, changes in protein phosphorylation, and variations in protein-protein interactions that occur either between different TRP isoforms or when TRP channel proteins interact with other unique proteins. Most of these topics have been extensively discussed in previous reviews [1, 3, 9, 10] and will not be further discussed here. The focus of this review will be on the regulation of TRP channel activity by protein phosphorylation.

Protein phosphorylation and dephosphorylation are common, reversible, posttranslational modifications that can regulate the structure and function of ion channels. A particular phosphorylation/dephosphorylation state can modify channel activity and thus alter the electrophysiological properties of excitable and non-excitable cells. A few well-known examples include protein kinase G (PKG) regulation of large conductance Ca^{2+} -dependent K^+ channels (BK_{Ca}) and the regulation of NMDA receptors by tyrosine phosphorylation. The BK_{Ca} channel is composed of four α -subunits that form the pore and a regulatory β -subunit; the channel is regulated by voltage in a Ca^{2+} -dependent manner. PKG phosphorylates the α -subunit at Ser-1072 near the C-terminus, shifting the Ca^{2+} sensitivity of the channel and producing hyperpolarization [11]. NMDA receptors are regulated in part by the opposing actions of protein tyrosine kinases and phosphotyrosine phosphatases. Src phosphorylates the NMDA receptor subunits and/or other proteins in the NMDA receptor complex, resulting in enhanced single-channel gating of NMDA receptors and as a consequence increases the NMDA receptor-mediated synaptic currents in neurons [12]. In last few years, rapid development in the field of TRP channel research has demonstrated an important role for protein phosphorylation in the regulation of TRP channels, particularly for the members of the TRPC, TRPV, TRPM, and TRPP subfamilies.

TRPC Channels

The TRPC subfamily contains seven members, which can be further divided into four subgroups: TRPC1, TRPC2, TRPC4,5, and TRPC3,6,7 [1, 3]. TRPC1 needs to form heteromultimeric complex with TRPC4 or TRPC5 for its proper trafficking to plasma membrane to form functional channels [6]. TRPC2 participates in pheromone sensory signaling and sperm fertilization [1], but in humans, TRPC2 is a pseudogene [1, 3]. TRPC3, 6 and 7 form a subfamily sharing amino acids identities

between 70 and 80%, whereas TRPC4 and 5 form another subgroup with unique characteristics of potentiation by lanthanides. Lanthanides are among the most commonly used inhibitors for non-selective cation channels. Surprisingly, they activate TRPC4, TRPC5, and the heteromer of TRPC1 and TRPC5 [1, 6]. TRPC channels are widely expressed in the nervous systems including the cortex, thalamus, hippocampus, cerebellum, brainstem, spinal cord and peripheral ganglia [6, 7, 13]. Functionally, TRPC1 and TRPC5 are believed to form the molecular basis of group 1 mGluR-activated cation channels [5, 6], whereas TRPC4 may influence the GABA release from dendrites of thalamic interneurons [14]. Furthermore, TRPC1, 3, 5, and 6 play crucial roles in the guidance of neuronal growth cones, including those in hippocampal neurons, cerebellar granule neurons, and spinal neurons [7, 8].

TRPC channels are activated by agonist- or growth factor-mediated stimulation of phospholipase C- β (PLC- β) and PLC- γ [1, 3]. Activation following PLC stimulation appears to be via diverse pathways. The activity of PLC generates inositol 1,4,5-trisphosphate (IP_3), which may induce IP_3 receptor-mediated Ca^{2+} release from intracellular Ca^{2+} stores. The resultant decrease in store Ca^{2+} content activates most TRPC channels via a capacitative mechanism under certain conditions [1, 9]. PLC activity also produces DAG, which activates TRPC3, 6, and 7, independent of Ca^{2+} store depletion [1, 3]. Regarding the regulation by phosphorylation, protein kinase C (PKC) and PKG both inhibit TRPC channels, except for TRPC1, which is activated by PKC. On the other hand, CaM-kinase II activates TRPC6; Src family non-receptor tyrosine kinases activate both TRPC3 and TRPC6 (table 1).

Phosphorylation of TRPC by PKC and PKG

Zhang and Saffen [15] provided the first evidence that TRPC6 activity is negatively regulated by PKC. They found that TRPC6, when overexpressed in CHO cells, was inhibited by phorbol 12-myristate 13-acetate (PMA), which activates PKC, and furthermore, the PMA-induced inhibition was abolished in the presence of GF109203X, a highly selective and potent inhibitor of multiple PKC subtypes. Similar studies by two other groups found that TRPC3, 4 and 5 were also inhibited by PKC in HEK293 or DT40 overexpression system [16]. Recently, Trebak et al. [17] identified Ser-712 in the TRPC3 amino acid sequences to be a specific PKC phosphorylation site. A point mutation at this site abolished the PKC phosphorylation on TRPC3 proteins and also markedly reduced the inhibitory effect of PKC on TRPC3-

Table 1. Phosphorylation regulation of TRPC channels

Gene name	Mode of activation	Phosphorylation and action
TRPC1	Capacitative, membrane stretch	PKC activates [24]
TRPC3	Capacitative, DAG	PKC and PKG inhibit [15–17, 20] Src activates [26]
TRPC4	Capacitative	PKC inhibits [16]
TRPC5	Capacitative?	PKC inhibits [16]
TRPC6	Capacitative? DAG	PKC and PKG? inhibit [15, 16, 20] Fyn and CaMKII activate [19, 25]
TRPC7	Capacitative, DAG	PKC and PKG? inhibit [16, 20]

mediated Ca^{2+} influx. Ser-712 is located within a consensus PKC phosphorylation sequence of -PS⁷¹²PKS-, which is conserved between two TRPC subfamilies, TRPC3,6,7 and TRP4,5, suggesting that the same site may be responsible for PKC-induced inhibition of TRPC4, 5, 6 and 7. Another study by Zhu et al. [18] found that PKC phosphorylates Thr-972 of mouse TRPC5, causing channel desensitization. Thr-972 resides in a VT⁹⁷²TRL motif that interacts with PDZ domains. It is possible that PKC phosphorylation at Thr-972 may disrupt the interaction of TRPC5 with PDZ domains of other proteins, such as NHERF, resulting in channel desensitization. TRPC6 and 7 are also desensitized by PKC [19]. Channel desensitization is expected to cause an overall reduction in Ca^{2+} influx. However, several lines of evidence suggest that different mechanisms may govern the channel desensitization observed by Zhu et al. [18] and the overall PKC-mediated inhibition of TRPC channels observed by many others [15–17]: (1) Thr-972 is only conserved between TRPC4 and 5 and therefore, this channel desensitization mechanism cannot apply to TRPC3, 6, and 7; (2) PKC-mediated general inhibition of TRPC is due to PKC phosphorylation on -PS⁷¹²PKS- [17], but disruption of this PKC site has no effect on channel desensitization [17].

PKG is another kinase capable of inhibiting TRPC3 activity [20]. Our recent studies have shown that the activation of PKG by cyclic GMP (cGMP) inhibits TRPC3-mediated Ca^{2+} influx in TRPC3-overexpressing HEK cells and that this inhibitory effect of cGMP is abolished by the PKG inhibitors KT5823 and H-8. Furthermore, disruption of two consensus PKG phosphorylation sites, Thr-11 and Ser-263, markedly reduces the inhibitory effect of cGMP. These data indicate that PKG phosphorylates TRPC3 at Thr-11 and Ser-263, and as a consequence, inactivates TRPC3 [20]. A protein sequence alignment shows that two PKG phosphorylation sites in TRPC3, -RRxT¹¹- and -RRKLS²⁶³MQC-, are both conserved in TRPC6 and 7, thus suggesting that PKG may

also inhibit them. An inhibitory action of PKC and PKG on TRPC may represent important negative feedback mechanisms in the control of cytosolic Ca^{2+} levels, thereby influencing Ca^{2+} -dependent processes in a variety of different cell types (fig. 1). In these negative feedback pathways, the activation of TRPC results in Ca^{2+} entry; a rise in cytosolic Ca^{2+} , together with elevated DAG levels, stimulates PKC activity, which feeds back to inactivate the TRPC channels [16] (fig. 1). The elevation of cytosolic Ca^{2+} also stimulates the activity of nitric oxide synthase (e.g., neuronal nitric oxide synthase), leading to increased production of cGMP. This second messenger activates PKG; the ensuing phosphorylation inhibits TRPC channel activity and completes a PKG-dependent negative feedback loop [20–22] (fig. 1). Recent studies from our group also demonstrated that these two negative feedback loops are connected: PKG is a downstream target of PKC [23]. Importantly, point mutations at two PKG phosphorylation sites (T11A and S263Q) of TRPC3 markedly reduce the PKC inhibition of TRPC3. Furthermore, inhibition of PKG activity by KT5823 (1 μM) or H8 (10 μM) also greatly reduces PKC inhibition of TRPC3. These data strongly suggest that PKC may also inhibit TRPC channels indirectly by activating PKG. Both PKC- and PKG-mediated negative feedback pathways may play important roles in the regulation of Ca^{2+} influx in neurons, and may serve to protect neurons from the detrimental effects of excessive NO, Ca^{2+} and PKC activation [16, 20–22]. However, the response of TRPC1 to PKC is very different from either TRPC3,6,7 or TRPC4,5. Contrary to other TRPC channels, TRPC1 is activated by direct PKC phosphorylation [24].

Src and TRPC3, 6

It has been known for a long time that tyrosine kinases are involved in the activation of capacitative Ca^{2+} influx [9], of which TRPC channels are among the major molecular candidates [1, 9]. Two recent studies have pro-

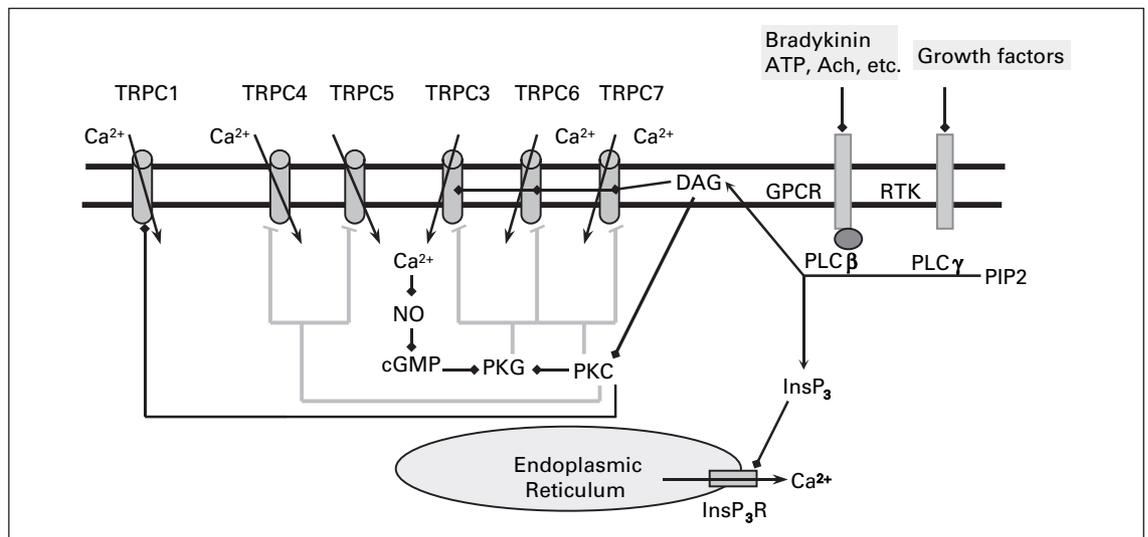


Fig. 1. Activation and PKC- and PKG-mediated regulation of TRPC channels. Agonists bind to either G-protein-coupled receptors (GPCR) or tyrosine kinase-linked receptors (RTK) to activate PLC- β or PLC- γ , leading to the production of diacylglycerol (DAG) and InsP₃. InsP₃ binds to its receptor (InsP₃R), resulting in store Ca²⁺ release and activating TRP-mediated capacitative Ca²⁺ entry. DAG activates some TRP channels such as TRPC3,6,7 via non-capacitative mechanism. DAG also activates PKC, which inhibits TRPC3,4,5,6,7 but stimulates TRPC1. A rise in [Ca²⁺]_i also activates PKG via NO/cGMP pathway. PKG then inactivates TRPC3,6,7 in a negative feedback mechanism. PKG can also be activated by PKC, leading to the inhibition of TRPC3,6,7. Black symbols (→), stimulatory processes; gray symbols (—/), inhibitory processes.

vided evidence that the Src family of non-receptor tyrosine kinases plays a key role in DAG-induced activation of TRPC3 and TRPC6 [25, 26]. Vazquez et al. [26] found that inhibition of Src kinases by genistein and erbstatin abolished the receptor- and OAG (a DAG analog)-induced activation of TRPC3. In addition, OAG failed to activate TRPC3 in cells that were either Src-deficient or expressed a dominant-negative mutant of Src, and furthermore, OAG activation of TRPC3 was restored after the cells were transfected with a Src-expressing construct. These results indicate an obligatory requirement for Src kinase in DAG-induced activation of TRPC3. Note that Src may not directly act on TRPC3. Instead, a concerted role for both DAG and Src seems to be necessary for TRPC3 activation, perhaps through a mechanism involving Src-dependent phosphorylation and/or recruitment of a yet unknown accessory/regulatory protein within the vicinity of TRPC3. In addition to TRPC3, the activation of TRPC6 by DAG may also involve Fyn (a Src family kinase) [25], whose SH2 domain physically associates with the N-terminal region of TRPC6. The associated Fyn directly phosphorylates TRPC6, and as a consequence, increases the activity of TRPC6 channel [25].

CaM-Kinase II and TRPC6

CaM-kinase II can activate TRPC6. In patch-clamp studies, Shi et al. [19] found that TRPC6, expressed in HEK293 cells, was activated by extracellular Ca²⁺, which could be prevented by either an organic CaM-kinase II inhibitor KN-62 or a CaM-kinase II-specific inhibitory peptide. These results suggest that CaM-kinase II-mediated phosphorylation is an obligatory step for TRPC6 channel activation. Surprisingly, the same study also found that inhibitors of CaM-kinase II failed to affect TRPC7, a close relative of TRPC6, suggesting that the regulation by CaM-kinase II may not be a universal mechanism for other TRPC channels.

TRPV Channel

The TRPV subfamily contains six members (TRPV1–6). TRPV1–4 channels are temperature-sensitive. Exogenous vanilloids such as capsaicin can activate TRPV1, whereas endogenous lipid signaling molecules such as anandamide and eicosanoid can activate TRPV1 and TRPV4 [27, 28]. TRPV5 and TRPV6 are only distinctly related to TRPV1–4 with a 30–40% sequence homology.

Table 2. Phosphorylation regulation of TRPV channels

Gene name	Mode of activation	Phosphorylation and action
TRPV1	Heat, vanilloids, anandamine, protons	PKA and PKC sensitize the responses to capsaicin, heat and anandamide [29–35]. CaMKII is required for activation by capsaicin [33]. PKA reduces desensitization [36–38]
TRPV2	Heat, membrane stretch	PKA potentiates the heat response [40]
TRPV4	Warm, osmotic cell swelling flow shear stress, 5'-6'-EET	PKC activates [41]. Tyrosine kinase activates [42, 43]?
TRPV5	Low intracellular Ca ²⁺ , hyperpolarization	SGK1 activates [44]
TRPV6	Low intracellular Ca ²⁺ , hyperpolarization	Src activates [46]. PKC reduces inactivation [45]

TRPV5 and TRPV6 have high selectivity for Ca²⁺ over Na⁺ ($P_{Ca}/P_{Na} > 100$), are mainly expressed in Ca²⁺-transporting epithelia, and are assumed to play an important role in Ca²⁺ (re)absorption by the kidney and intestine [1]. The activity of many TRPV channels can also be modulated by protein phosphorylation (table 2).

Phosphorylation of TRPV1 by PKC, Protein Kinase A (PKA), and CaM-Kinase II

TRPV1 is a non-selective cation channel expressed predominantly in nociceptive sensory neurons, and the channel is known to play a major role in mediating inflammatory and thermal nociception. Mice lacking TRPV1 display reduced thermal hyperalgesia following inflammation or local injection of bradykinin and nerve growth factor [27]. Multiple kinases are known to regulate TRPV1. PKC phosphorylates Ser-502 and Ser-800 in rat TRPV1, and as a result, either potentiates or sensitizes responses of this channel to capsaicin, heat, and anandamide [29–32]. In addition, CaM-kinase II phosphorylates rat TRPV1 on Ser-502 and Thr-704, and the phosphorylation is required for channel activation by capsaicin [33]. PKA may also phosphorylate TRPV1 on Ser-502, and as a consequence, sensitizes the response of TRPV1 to both heat [34] and capsaicin [35]. Protein phosphorylation may also modulate the desensitization process of TRPV1, thereby affecting adaptation during pain perception. Amino acid residues Thr-370 and Ser-116 in rat TRPV1 appear to be particularly important in this regard. PKA can phosphorylate Thr-370 and Ser-116, reducing desensitization. On the other hand, calcineurin can dephosphorylate Thr-370, facilitating desensitization [36–38].

Regulation of TRPV2 and TRPV4 by Phosphorylation

TRPV2 and TRPV4 are two temperature-sensitive channels with activation thresholds of ≥ 53 and ≥ 25 –

27°C, respectively [39]. Functionally, TRPV2 is believed to be involved in the sensory response to noxious temperatures, whereas TRPV4 appears to be related to thermosensing, mechanosensing, neuropathic pain, and vascular regulation [28, 39]. TRPV2 is a substrate of PKA. In most cells, PKA interacts with TRPV2 through a PKA-binding protein named ACBD3 [40]. PKA phosphorylation enhances TRPV2-mediated Ca²⁺ influx in response to heat [40]. On the other hand, the activity of TRPV4 is stimulated by PKC [41], although it is unclear whether this stimulation is due to direct PKC phosphorylation on TRPV4 proteins. One study suggested that TRPV4 is regulated by tyrosine phosphorylation [42], but this finding has been disputed [43].

Regulation of TRPV5 and 6 by SGK1, PKC and Src

TRPV5 is activated by serum and glucocorticoid-inducible kinase, SGK1. This stimulatory effect is due to enhanced TRPV5 abundance in the plasma membrane, requiring the presence of the scaffold protein, NHERF2 [44]. On the other hand, the activity of TRPV6 can be regulated by calmodulin and PKC. Binding of Ca²⁺-dependent calmodulin to TRPV6 inactivates the channel, which is countered by PKC-mediated phosphorylation of TRPV6 [45]. Thus, by altering the inactivation behavior of TRPV6, PKC-mediated phosphorylation acts as a switch to regulate the amount of Ca²⁺ influx through TRPV6 [45]. TRPV6 can also be activated by the Src tyrosine kinase, which is counterbalanced by the protein tyrosine phosphatase 1B [46]. Taken together, TRPV6 activity is closely controlled by both the calmodulin/PKC system and the tyrosine kinase/phosphatase system [45, 46].

Table 3. Phosphorylation regulation of TRPM and TRPP channels

Gene name	Mode of activation	Phosphorylation and action
TRPM4	Ca ²⁺ -activated, voltage-gated, mechanic pressure	PKC sensitizes the responses to Ca ²⁺ [48]
TRPM7	Oxidative stress, Mg ²⁺ -ATP	PKA and Src activate [51, 52]
TRPP1	Flow shear stress, not a channel by itself	Tyrosine kinase inhibits TRPP1 interaction with pp125FAK [59]
TRPP2	Ca ²⁺ , protons, complex with TRPP1	CK2 sensitizes the responses to Ca ²⁺ and facilitates the retrieval of TRPP2 into intracellular compartment [61, 62]

TRPM Channels

The TRPM subfamily consists of eight members (TRPM1–8). The C-terminal sequences of the TRPM family vary in both length and structure. Three members of the TRPM subfamily (TRPM2, TRPM6 and TRPM7) have enzymatic activity [1]. TRPM2 has a nucleoside diphosphatase domain that binds specifically to and hydrolyzes ADP-ribose, whereas TRPM6 and TRPM7 contain α -kinase domains. TRPM channels have more diverse ion selectivities than other TRP channels. TRPM2, TRPM3, and TRPM8 are Ca²⁺-permeable channels, whereas TRPM4 and TRPM5 are impermeable to Ca²⁺. TRPM6 and TRPM7 are primarily responsible for Mg²⁺ transport. Regulation of TRPM by phosphorylation is summarized in table 3.

Phosphorylation of TRPM4 by PKC

TRPM4 is a voltage-dependent, Ca²⁺-impermeable cation channel. Opening of this channel depolarizes the membrane. The channel is activated by intracellular Ca²⁺, but the currents decay rapidly due to decreased sensitivity of the channels to Ca²⁺. PMA, an activator of PKC, increases the activity of TRPM4 [47] by enhancing the sensitivity of TRPM4 to Ca²⁺ [48]. Disruption of two PKC phosphorylation sites, Ser-1145 and Ser-1142, abolishes the PMA-induced activation of human TRPM4, indicating that the channel activation is due to direct PKC phosphorylation on these sites [48].

Regulation of TRPM7 by Src and PKA

TRPM7 is highly permeable to Mg²⁺ [1, 49], and is therefore crucial for Mg²⁺ homeostasis. The channel is associated with cell proliferation, cell survival, and anoxic neuronal death [1, 50]. TRPM7 contains an atypical α -kinase domain in its C-terminal region, but the specific function of this kinase is unclear [1]. One possible role for this kinase domain is to mediate the effects of cAMP and PKA, both of which enhance channel activity [51]. Sepa-

rately, there is strong evidence that the TRPM7 channel is activated by the Src tyrosine kinase in rat brain microglia [52]. Because Src family tyrosine kinases are coupled to multiple receptor-mediated pathways, it is reasonable to speculate that TRPM7 may allow Ca²⁺ and Mg²⁺ entry in response to stimulation by tyrosine kinase-coupled receptor, thereby participating in various cellular responses.

TRPP Channels

There are four members in the TRPP subfamily, TRPP1–3 and TRPP5 [1, 2]. TRPP2, TRPP3 and TRPP5 share sequence homology with other TRP channel subfamilies and function as Ca²⁺-permeable cation channels [1, 2]. The best known TRPP channels are TRPP1 (PKD1) and TRPP2 (PKD2). Mutations in either of these two genes result in autosomal dominant polycystic kidney disease (ADPKD), an inherited disorder that is one of the primary causes of renal failure in humans [53]. TRPP2 and Lov-1 (a homolog of human TRPP1) are expressed in ciliated sensory neurons of *Caenorhabditis elegans*, and are necessary for male sensory behaviors [54]. There is a general lack of information on the functional roles of TRPP1 and TRPP2 in the mammalian nervous system and many other systems, partly because of the low level of endogenous TRPP1 expression in native cells [55]. Regulation of TRPP by phosphorylation is summarized in table 3.

Regulation of TRPP1 and 2 by Tyrosine Phosphorylation and Casein Kinase 2 (CK2)

TRPP1 is phosphorylated by tyrosine kinase [56, 57] and PKA [57, 58]. Tyrosine phosphorylation facilitates the interaction of TRPP1 with E-cadherin, but inhibits the interaction of TRPP1 with focal adhesion kinase (pp125FAK) [59]. The overall phosphorylation level of TRPP1 is elevated in ADPKD patients, and this over-

phosphorylation may interfere the interaction of TRPP1 with TRPP2/E-cadherin/ β -catenin, and cause the depletion of both TRPP1 and E-cadherin from the plasma membrane [60].

For TRPP2, phosphorylation of Ser-812 appears to be particularly important. Cai et al. [61] found that Ser-812 phosphorylation by CK2 significantly increases the Ca^{2+} sensitivity of TRPP2 channels. Another recent study found that Ser-812 phosphorylation by CK2 and dephosphorylation by protein phosphatase 2A directs the trafficking of TRPP2 to distinct subcellular compartments [62]. Phosphorylated TRPP2 binds to either PACS-1 (phosphofurin acidic cluster sorting protein-1) or PACS-2. The binding to PACS-2 causes TRPP2 to be retrieved from the intermediate compartment back to the endoplasmic compartment. On the other hand, the binding to PACS1 causes the retrieval of TRPP2 to the Golgi compartment.

Concluding Remarks

TRP channels are widely expressed in the central and peripheral nervous systems [2, 4, 6, 13, 39]. Protein phosphorylation has been shown to regulate multiple TRP

channels with diverse consequences (tables 1–3). In most cases, phosphorylation leads to increased channel activity. For example, PKC phosphorylation increases the activity of TRPC1 [24] and TRPM4 [47, 48]; the non-receptor tyrosine kinase Fyn directly phosphorylates and activates TRPC6 proteins [25]; on the other hand, PKC and PKG inhibit multiple TRPC channels and such inhibition may represent important negative feedback mechanisms for the tight control of cytosolic Ca^{2+} levels in many cell types.

The physiological significance of the regulation of TRP channels by phosphorylation is fascinating. TRP channels play diverse functional roles, including thermal sensation, nociception, mechanosensing, growth cone guidance, inflammatory responses, membrane potential control and Mg^{2+} homeostasis. Various kinases and phosphatases may regulate the activities of different TRP channel isoforms, providing enormous control on diverse cellular processes.

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