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Review

Modulation of low-voltage-activated T-type Ca^{2+} channels ☆

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ABSTRACT

Low-voltage-activated T-type Ca^{2+} channels contribute to a wide variety of physiological functions, most predominantly in the nervous, cardiovascular and endocrine systems. Studies have documented the roles of T-type channels in sleep, neuropathic pain, absence epilepsy, cell proliferation and cardiovascular function. Importantly, novel aspects of the modulation of T-type channels have been identified over the last few years, providing new insights into their physiological and pathophysiological roles. Although there is substantial literature regarding modulation of native T-type channels, the underlying molecular mechanisms have only recently begun to be addressed. This review focuses on recent evidence that the Cav3 subunits of T-type channels, Cav3.1, Cav3.2 and Cav3.3, are differentially modulated by a multitude of endogenous ligands including anandamide, monocyte chemoattractant protein-1, endostatin, and redox and oxidizing agents. The review also provides an overview of recent knowledge gained concerning downstream pathways involving G-protein-coupled receptors. This article is part of a Special Issue entitled: Calcium channels.

Contents

Abbreviations: LVA, low-voltage-activated; HVA, high-voltage-activated; T-type channels, T-type Ca^{2+} channels; cAMP, cyclic adenosine monophosphate; PKA, protein kinase A; PKC, protein kinase C; PKG, protein kinase G; PTK, protein tyrosine kinase; HEK293, human embryonic kidney 293; CHO cells, Chinese hamster ovary cells; OAG, 1-oleoyl-2-acetyl-sn-glycerol; DAG, diacylglycerol; PLC, phospholipase C; CaMKII, calmodulin-dependent protein kinase II; KCa3.1, Ca^{2+}-activated K^+ channels of intermediate conductance; Kv, voltage-activated potassium channels; NK1, neurokinin 1; MCP-1, monocyte chemoattractant protein-1; GHRH, growth-hormone-releasing hormone; KLHL1, Kelch-like 1; AEA, N-acyl ethanolamides; PUFA, polyunsaturated fatty acids; GPCR, G-protein-coupled receptor; $G_{\beta\gamma}$, G-protein βγ subunits; CCR2, chemokine receptor 2; NMUR1, neuromedin U type 1 receptor; CRFR1, corticotrophin releasing factor receptor 1

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1. Introduction

Ca^{2+} is a ubiquitous intracellular second messenger critical for cellular functions [1]. The elevation of free intracellular Ca^{2+} ($[Ca^{2+}]_i$) levels triggers various responses including the activation of Ca^{2+} dependent enzymes, the secretion of neurotransmitters and hormones, muscle contraction, as well as affecting cell proliferation, differentiation and apoptosis [1,2]. Voltage-gated Ca^{2+} channels, essential mediators of rapid influx of extracellular Ca^{2+} into the cytosol of electrically excitable cells, are generally categorized into two groups: high-voltage-activated (HVA) and low-voltage-activated (LVA) Ca^{2+} channels [3]. Members of the HVA Ca^{2+} channel family include the L-, N-, P/Q- and R-types, typically require stronger membrane depolarization to initially open and exhibit a wide spectrum of pharmacological and biophysical properties. The HVA channels are heteromultimers comprising a pore-forming α_1 subunit that defines the Ca^{2+} channel subtype, together with ancillary β and $\alpha_2\delta$ subunits that co-assemble to form a functional Ca^{2+} channel complex [4]. In contrast, functional LVA Ca^{2+} channels (called T-type) appear to consist of a single α_1 subunit. Distinct from the HVA channels, T-type channels exhibit properties of low unitary conductance, fast inactivation and slow deactivation kinetics, and negative steady-state inactivation at physiological resting potentials [5].

The ten Ca^{2+} channel α_1 subunits in the mammalian genome are structurally similar, composed of four homologous domains (I–IV), each of which contains six transmembrane helices (S1 through S6) plus a re-entrant pore-forming loop that permits the selective passage of Ca^{2+} ions. The S4 segment in each domain contains positively charged amino acids residues in every third or fourth position and forms part of the voltage sensor, driving the channel to open and close in response to membrane potential changes. The four major domains are linked by different sized cytoplasmic regions and the N- and C-termini are also modeled to be localized on the cytoplasmic side. In vertebrates, the T-type Ca^{2+} channel family encompasses three α_1 subunit genes, CACNA1G, CACNA1H and CACAN1I, which respectively encode α_{1G} (Cav3.1), α_{1H} (Cav3.2), and α_{1I} (Cav3.3) isoforms [6–10]. Each T-type isoform exhibits unique biophysical and pharmacological profiles as well as distinct cellular and subcellular distributions [2,11–17]. The Cav3.1 and Cav3.2 currents are highly reminiscent of prototypical LVA currents recorded in native cells while Cav3.3 currents display distinctly slower inactivation kinetics [6,10,18–20]. Alternative splicing notably enhances the potential diversity of T-type channel isoforms [11,18,21] and there is growing evidence for significant differences in the biophysical properties of the various splice variants [22–24]. The unique set of biophysical properties of T-type channels, especially their negative voltage-dependent properties and ability to generate "window" Ca^{2+} currents at or near resting membrane potentials, makes them ideally suited towards regulating cellular excitability and oscillatory behaviors.

In the heart, Cav3.1 and Cav3.2 are the predominant T-type isoforms. The channels are more prevalent in the early development and they disappear in the myocardium shortly after birth and are localized to the pacemaker tissue in adult hearts, where they have an established role in pacemaker function [25]. Genetically modified mouse models have shed additional light on the respective roles of T-types in the pathogenesis of left ventricle cardiomyopathy. For example, the Cav3.1 knockout mice display a depression in heart rate and slower pacemaker activity in isolated atrial pacemaker myocytes [26]. The complete lack of LVA currents in the atria of these mice indicates that the Cav3.1 channels are the primary LVA pacemaker channels [26] and are important for maximal pacing rates [27,28]. In neurons, relatively small membrane depolarization can trigger the opening of T-type channels with the ensuing Ca^{2+} entry serving to further depolarize the plasma membrane and initiate action potential bursts [12]. The physiological significance of T-type properties are underscored by their well-documented roles in regulating neuronal firing patterns under both normal physiological conditions such as sleep [12,29–31] and in pathophysiological conditions such as epilepsy [32]. Of note, both T-type channel biophysical properties and their associated physiological activities are modulated by a wide range of cellular mechanisms and pathways (Fig. 1). Understanding these various pathways and mechanisms may identify novel strategies for modulating T-type channel activity for the purpose of therapeutic intervention. The current review focuses on recent advances in our understating of T-type Ca^{2+} channel modulation.

2. Protein kinase-mediated T-type channel modulation

2.1. Protein kinase A

A large amount of literature suggests that native T-type channels are differentially regulated by protein kinase A (PKA) activity. As examples, in NIH 3T3 cells, an increase in T-type currents induced by acetylcholine is abolished in the presence of Rp-cAMP, a PKA inhibitor [33]. Forskolin and 8-Br-cAMP reproduce the effect of acetylcholine confirming the involvement of PKA in the increased T-type current [33]. In sheep pituitary somatotropes, the growth-hormone-releasing hormone (GHRH)-mediated increase in T-type current is abolished by Rp-cAMP and another PKA inhibitor, H89 [34]. However, in the latter study, the direct effect of PKA activation was not reported and no shift in the steady-state activation curve was been described [34]. In frog atrial myocytes, intracellular cAMP increases basal T-type currents [35]. Similarly, in rat adrenal glomerulosa cells, a T-type current increase induced by serotonin through the 5-HT_7 receptor is prevented by H89 and it is mimicked by cAMP [36].

T-type currents resulting from all three cloned channels (Cav3.1, Cav3.2 and Cav3.3) have similarly been shown to be up-regulated by PKA activity [37]. In *Xenopus oocytes* co-expressing cloned Cav3.2 and 5-HT_7 cDNAs, serotonin induced a significant increase of Cav3.2 currents without altering the activation profile [38]. The effect of serotonin was prevented by the PKA inhibitors, H89 and PKI, whereas 8-Br-cAMP and forskolin reproduced 5-HT_7 effects. Utilizing a chimeric construct approach, the Cav3.2 domain II–III linker region was necessary for mediating PKA effects [38]. Interestingly, mutating putative PKA sites in the Cav3.2 II–III linker did not alter PKA-dependent regulation. Furthermore, 8-Br-cAMP and forskolin effects were found to be relatively slow, suggesting that some other mediator rather than the Cav3.2 channel itself might be the substrate for phosphorylation by PKA [38–40]. Of note however, some of the differences between modulation studies may reflect experimental and/or cell-type differences. For example, while the current density for all three T-type isoforms exogenously expressed in mammalian cells (Cav3.1, Cav3.2 and Cav3.3) is enhanced by activation of cAMP, the effect was observed only at 37 °C and not at room temperature. Further, a direct PKA-dependent phosphorylation of the Cav3.2 subunit was observed at 37 °C but not at room temperature, perhaps reflecting the temperature-sensitive nature of kinase translocation [37]. Additional cell-type and Cav subunit-specific interactions with scaffolding and

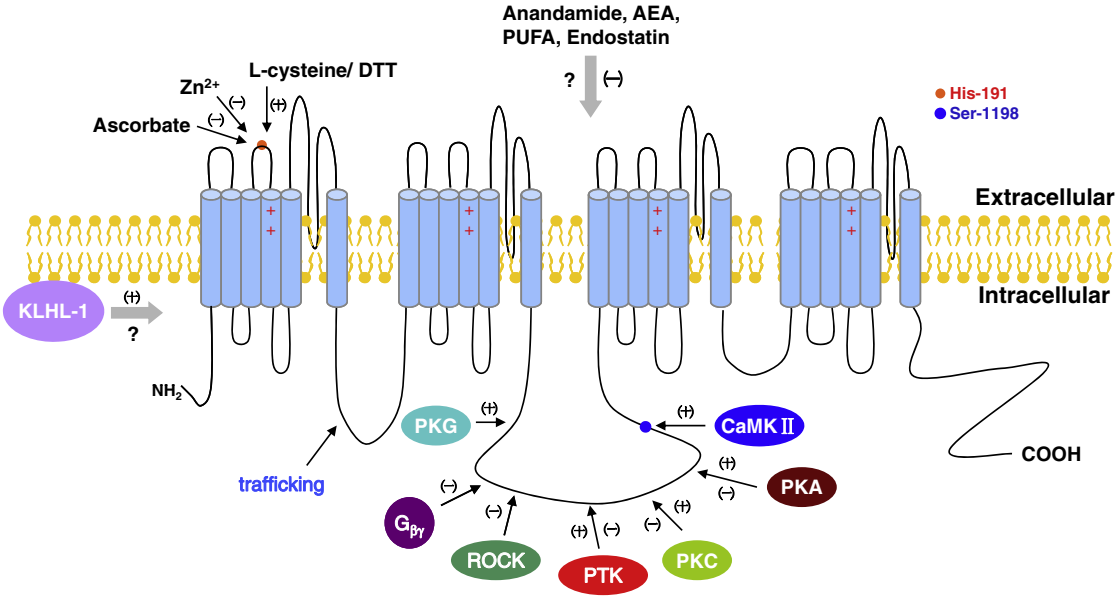

Fig. 1. Schematic representation of recently identified pathways for Cav3 channel modulation. Abbreviations: CaMKII, calmodulin-dependent protein kinase II; PKA, protein kinase A; PKC, protein kinase C; PKG, protein kinase G; PLC, phospholipase C; PTK, protein tyrosine kinase; $G_{\beta\gamma}$, G-protein βγ subunits; KLHL-1, Kelch-like 1; AEA, N-acyl ethanolamides, PUFA, polyunsaturated fatty acids.

other proteins may also come into play. For example, caveolin-3 interacts with Cav3.2 but not Cav3.1 channels to regulate PKA-dependent modulation in neonatal ventricular myocytes [41].

Distinct from the above PKA-mediated up-regulation of T-type current activity, in bass retinal horizontal cells T-type currents are inhibited by dopamine, an effect prevented by PKA inhibitors and mimicked by 8-CPT, a cAMP analogue [42,43]. Similarly, in newt olfactory receptor cells adrenaline inhibits T-type currents, an effect mimicked by 8-Br-cAMP, forskolin and by intracellular application of the catalytic subunit of PKA [44]. In mouse dorsal root ganglion (DRG) neurons the activation of neuromedin U type 1 receptor (NMUR1) inhibits T-type currents, an effect which is abolished by pretreatment with H89 or intracellular application of PKI. The inhibition of T-type currents by NMUR1 is accompanied by a shift of the inactivation curve towards more negative potentials without effect on the activation profile [45]. Similar results have been demonstrated for activation of muscarinic M4 receptors [46]. In contrast to that for native T-type currents, the inhibition of recombinant Cav3.2 currents by dopamine D1 receptor activation persists in the presence of PKI and inclusion of the catalytic subunit of PKA in the patch-pipette produces no effect [39], a result consistent to that observed with 8-Br-cAMP alone [40]. Moreover, native T-type channels appear insensitive to cAMP in certain cell types, including adrenal glomerulosa cells, pituitary lactotroph cells [47–49], mouse DRG neurons, rat nodose ganglion and NG108-15 cells [50–54]. Together, results suggest that the PKA regulatory effects on native and recombinant T-type currents is highly variable across cell types, interacting proteins, temperature and via functionally coupling to different G-protein coupled receptor pathways (Table 1).

2.2. Protein kinase C

A number of studies have shown that T-type channels can be either up- or down-regulated by the activation of protein kinase C (PKC). In rat pituitary GH3 cells, a Ni^{2+}-resistant T-type current is inhibited by the lipid diacylglycerol (DAG) analogue 1-oleoyl-2-acetyl-sn-glycerol (OAG) [55]. Similar results have been reported for a Ni^{2+}-sensitive T-type current in both chicken DRG neurons [56], rat hippocampal neurons [57,58], canine cardiac Purkinje and ventricular cells and rat DRG neurons [59,60]. At least for exogenously expressed T-type channels, the effect of PKC activation appears to be non-specific as PMA elevates current density for all three T-type isoforms (Cav3.1, Cav3.2 and Cav3.3), albeit in a highly temperature-dependent manner [37,61]. Furthermore, in rat adrenal glomerulosa cells, phorbol esters and DAG analogues inhibit T-type currents by shifting the activation curve to positive potentials [62]. These effects mimic those of angiotensin II (Ang II) in these cells and the presence of PKC inhibitors abolishes Ang II-induced T-type current inhibition [62]. In NIH 3T3 cells, phorbol 12,13-dibutyrate (PdBU) inhibits T-type currents [33]. Activation of muscarinic M1 receptor does not modulate T-type currents, but activates PKA. In the presence of PKC inhibitors, M1 receptor activation increases T-type currents via a PKA-dependent pathway, which suggests cross-talk between PKA and PKC downstream of the muscarinic M1 receptor [33]. Similar findings have been reported in bass retinal horizontal cells [42], where dopamine inhibits T-type currents via both PKA and PKC pathways. In mouse DRG neurons, recent studies show that activation of muscarinic M3 receptors by a short-chain postsynaptic

Table 1
Summary of functional consequences of T-type channels modulated by GPCRs.

Regulatory pathways	G-protein-coupled receptors	Effects	References
Protein kinases			
PKA	Muscarinic M3 receptor, growth hormone-releasing hormone receptor, 5-HT_7 receptor	Enhancement	[33,34,38]
	Neuromedin U type 1 receptor, adrenaline, muscarinic M4 receptor	Inhibition	[44–46]
PKC	Angiotensin II type 1 receptor, endothelin-1 receptor,	Enhancement	[62,64]
	Muscarinic M3 receptor, neurokinin 1 receptors	Inhibition	[63,71]
PTK	Angiotensin II type 2 receptor	Inhibition	[49]
CaMKII	Noradrenaline	Enhancement	[60]
Rho kinase	Lysophosphatidic acid receptors	Inhibition	[74]
Novel receptor-mediated pathways			
$G_{q/11}$ and $G_{\beta\gamma}$	Muscarinic M1 receptor	Inhibition	[121]
$G_{\beta\gamma}$	Corticotrophin releasing factor type 1 receptor	Inhibition	[72]
$G_{\beta2\gamma2}$	Dopamine D1 receptor	Inhibition	[122]

α-neurotoxin inhibits T-type currents through a novel PKC isoform pathway [63].

A PKC-induced increase in a Ni^{2+}-sensitive T-type current has also been reported [64,65]. In cultured neonatal rat ventricular myocytes, endothelin-1 induces an increase in T-type currents that can be prevented by PKC inhibitors H7 and staurosporine and mimicked by PMA and PdBU [64]. In *Xenopus* oocytes expressing recombinant Cav3 channels, PMA induced an increase in Cav3.2 T-type currents without changes in biophysical properties, and which was attenuated by pre-incubation with various PKC inhibitors [65]. Interestingly, a similar PKC-dependent effect was not reproduced in mammalian cells and therefore modulation may depend upon cell type, interacting anchoring proteins and temperature [66]. Finally, some studies also report no effect of phorbol esters or DAG analogues on T-type currents, albeit HVA Ca^{2+} currents are modulated [67–70].

Rangel and colleagues describe a new mechanism wherein GPCRs modulate the Cav3.2 T-type channel [71]. The authors report that activation of the neurokinin 1 (NK1) receptor leads to reversible inhibition of recombinant human Cav3.2 channels transiently expressed in HEK293 cells. Using a combination of pharmacological and molecular approaches, Cav3.2 inhibition is shown to be mediated by a voltage-independent process involving the sequential activation of $G_{q/11}$ subunits, phospholipase C β (PLC_β) and PKC. These results differ with those reported by Wolfe et al. [39], who showed that inhibition of Cav3.2 channels by dopamine D1 receptors (another $G_{q/11}$ protein-coupled receptor) expressed in the adrenocarcinomal cell line H295R is mediated by direct interaction of $G_{\beta 2\gamma 2}$ subunits with the α subunit of Cav3.2. Further, Tao et al. [72], reported that corticotrophin releasing factor receptor 1 (CRFR1) specifically inhibits recombinant Cav3.2 channels in HEK293 cells by a pathway that involves neither $G_{q/11}$ nor PKC. Discrepancies across these studies may be due to the cell type and/or GPCR pathway specificity (Table 1). In addition, it is possible that cell-specific differences in alternative splice variants of the T-type channels could lead to the activation of distinct signaling pathways and result in different downstream responses.

2.3. Protein kinase G

In newt olfactory receptor cells, a Ni^{2+}-sensitive T-type current is increased when cGMP is applied in the patch-pipette [73]. The effect on T-type currents is mimicked by application of either the cGMP phosphodiesterase inhibitor, zaprinast, or the permeant cGMP analogue, CPT-cGMP. In addition, the selective cGMP-dependent protein kinase inhibitor, KT5823, abolishes cGMP-induced effects [73]. The cGMP-mediated increase in the olfactory receptor cells T-type current is associated with a hyperpolarizing shift in the activation curve without altering inactivation kinetics. Contrastingly, a Ni^{2+}-sensitive T-type current in NG108-15 cells was not affected by application of either cGMP or 8-Br-Cgmp [49,52].

2.4. Rho/Rho-kinase

Application of lysophospatidic acid (LPA) acts through activation of Rho kinase to mediate a reversible inhibition of transiently expressed Cav3.1 and Cav3.3 channels and with a shift to more depolarized potentials of the activation and inactivation profiles for the Cav3.2 channel [74]. LPA is known to act on LPA receptors, a family of GPCRs that are highly promiscuous in their coupling to downstream effectors [75], including activation of Rho kinase and ROCK [74]. Interference with LPA receptor coupling to the Rho kinase pathway using dominant-negative inhibitors of $G_{\alpha 12}$ and $G_{\alpha 13}$ signaling, inactivation of RhoA, or pharmacological inhibition of ROCK prevents the LPA-mediated modulation. In the Cav3.1 subtype, the site of action of Rho kinase has been localized to two clusters of serines and threonines within a highly conserved region of the domain II–III linkers [74] (Table 1). The physiological implications of Cav3.1 regulation by Rho kinase is likely underscored by the wide distribution of this T-type channel in the central nervous system [15]. Recently it has been shown that ROCK inhibitors mediate a reduction of seizures in mice [76,77], pointing to a possible role for the Rho/Rho-kinase signaling pathway in epilepsy. LPA receptor activation has also been linked to neuropathic pain [77], although it remains to be determined whether this involves altered Cav3.2 channel function.

2.5. Calmodulin-dependent protein kinase II

The Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) pathway is implicated in T-type channel modulation. In canine ventricular and Purkinje cells, a decrease in $[Ca^{2+}]_i$ results in a significant decrease of T-type currents [60]. By using ethylene glycol tetraacetic acid (EGTA) to buffer $[Ca^{2+}]_i$ in these cells, Tseng and colleagues concluded that a noradrenaline induced T-type current increase results from an increase in $[Ca^{2+}]_i$ [60] (Table 1). Native Cav3.2 currents in bovine adrenal glomerulosa cells are also increased by elevating $[Ca^{2+}]_i$ [78,79]. Incremental changes in $[Ca^{2+}]_i$ significantly enhance T-type currents by a hyperpolarizing shift in the activation profile. This effect is dependent upon CaMKII phosphorylation since it is abolished by either KN-62, a CaMK antagonist, or a specific CaMKII peptide inhibitor [48,79,80]. In the absence of increased $[Ca^{2+}]_i$, perfusion of a purified CaMKII mutant increases T-type currents in the presence of adenosine triphosphate [80].

Recombinant Cav3.2 T-type channels expressed in HEK293 cells have also been shown to be modulated by CaMKII [81]. As observed with native Cav3.2 currents, a rise in $[Ca^{2+}]_i$ induces a shift of the activation profile to more negative potentials without changes in inactivation [81]. Interestingly, the Cav3.1 T-type appears not to be modulated by either a rise in $[Ca^{2+}]_i$ or CaMKII activation [81]. Utilizing reconstituted chimeric constructs Barrett and colleagues identified that domain II–III linker of Cav3.2 as the target for CaMKII modulation [82]. Indeed, currents resulting from chimeric Cav3.1 channels containing the Cav3.2 II–III linker were increased by a rise in $[Ca^{2+}]_i$ while chimeric Cav3.2 channels containing the Cav3.1 domain II–III linker were not modulated. Cav3.2 domain II–III serine residues 1198 and 1153 are phosphorylated by CaMKII and mutation of serine 1198 to alanine abolishes the CamKII-dependent modulation [82]. In contrast, in mouse spermatogenic cells calmodulin (CaM) antagonists decrease a Ni^{2+}-sensitive T-type current [83] independently of CaMKII activation [84]. Application of the CaM inhibitor W7, but not the weaker antagonist W5, inhibits T-type currents and the effects of W7 are attenuated by either including CaM into the patch pipette or substituting extracellular Ca^{2+} by Ba^{2+}. In these cells, CaMKII activation is not involved in W7 mediated T-type current inhibition since the CaMKII inhibitor KN-62 does not reproduce the W7 effects. While further studies are required, it is possible that CaM can directly modulated T-type channels [84,85].

2.6. Protein tyrosine kinases

T-type channels are subject to modulation by certain protein tyrosine kinases (PTK). In mouse spermatogenic cells, a Ni^{2+}-sensitive T-type current is increased by PTK inhibitors tyrphostin A47 and A25 while tyrosine phosphatase inhibitors phenylarsine oxide and sodium orthovanadate inhibit T-type currents [86]. In contrast, the PTK inhibitors genistein and lavendustin A inhibit a Ni^{2+}-sensitive T-type current in NG108-15 cells [87]. This latter study does not describe the effect of PTK activators or tyrosine phosphatase inhibitors, and direct effects of PTK inhibitors on T-type currents cannot be completely excluded. Interestingly, extracellular application of genistein, a PTK inhibitor, has been shown to decrease T-type currents [72]. The inhibitory effect of genistein is associated with a hyperpolarizing shift in the voltage-dependence of inactivation. Genistein inhibits Cav3.1 currents in transiently transfected HEK293 cells independently

of PTK activity [88]. In addition, Cav3.1 channels expressed in HEK293 cells are not modulated by PTKs, since the PTK inhibitor tyrphostin AG213 and the catalytically active PTK p60C-SRC have no effects [88]. Interestingly, Cav3.3 channels expressed in HEK293 cells are directly blocked by the PTK inhibitor imatinib-mesylate [89] although they appear not to be affected by another PTK inhibitor, genistein [72]. Finally, both sodium orthovanadate, a tyrosine phosphatase inhibitor and intracellular application of an antibody against tyrosine phosphatases prevent the decrease of T-type currents induced by Ang II in NG108-15 cells [49] (Table 1). Importantly, it should be noted that these compounds had no effect on basal T-type currents in this latter study.

3. Protein kinase-independent modulation of T-type channels

3.1. Redox, zinc and oxidizing agents

T-type $Ca2^+$ channels are notable in their being modulated via several signaling pathways that do not involve classical intracellular messengers or protein kinases. Reducing agents such as the endogenous amino acid L-cysteine both up-regulate T-type currents in nociceptive neurons and trigger the development of hyperalgesia [77] likely due to an increase in excitability [90]. This type of redox-dependent modulation has also been demonstrated for T-type currents in reticular thalamic neurons and appears to occur selectively on Cav3.2 channels [91]. Conversely, certain oxidizing agents selectively inhibit Cav3.2 channels [92]. For example, both T-type current inhibition and the inhibition of reticular thalamic burst-firing are observed upon application of endogenous nitrosothiol reagents such as L-nitrosocysteine [92] and by oxidizing agents such as ascorbate [93]. In the case of ascorbate, the mechanism of action involves oxidization of a unique histidine residue (His-191) located in the Cav3.2 domain I S3 and S4 loop. Interestingly, the same His-191 residue is involved in the augmentation of Cav3.2 currents in response to L-cysteine, which is able to prevent blockade of the channel by endogenous zinc ions that normally inhibit Cav3.2 channel activity due to binding to extracellular histidine residues [94].

It should also be noted that in addition to a potent zinc-mediated inhibition of Cav3.2 channels, zinc ions cause slowing of Cav3.3 tail currents, which culminates in increased Cav3.3 channel activity during action potential bursts [95]. These observations are particularly interesting when considering recent findings showing that the interference with endogenous zinc ions can alter the occurrence and frequency of epileptiform discharges [96]. The authors suggest that this is the result of zinc-mediated modification of the gating kinetics of Cav3.3, a T-type isoform highly expressed in certain thalamic neurons. Interestingly, lead ions have been recently shown to have an excitatory effect on T-type activity and thereby on action potential firing of pyramidal neurons in the CA1 region of rat hippocampal slices [97]. This effect appears to involve the release of Ca^{2+} from the internal stores through inositol trisphosphate and ryanodine receptors.

3.2. Anandamide

Anandamide, an endogenous cannabinoid, inhibits both T-type native currents in NG108-15 cells and all three recombinant T-type isoforms transiently expressed in HEK293 cells [98]. Inhibition is specific to anandamide since 2-AG, another endogenous cannabinoid, and δ9-THC, the major psychoactive component of marijuana, both have no effect on T-type currents. Of note, anandamide inhibits T-type channels independent of both cannabinoid receptors and protein kinases, acts from intracellular side of the membrane, and inhibition persists in the presence of GDP-β-S. Anandamide accelerates T-type current inactivation kinetics and shifts steady-state inactivation properties towards more negative potentials [98]. Fatty acids such as arachidonic acid, as well as other N-acyl ethanolamides and various polyunsaturated fatty acids, similarly inhibit T-type channels in the micromolar range through a membrane-delimited, possibly direct interaction [40,47,99].

3.3. Monocyte chemoattractant protein-1

Monocyte chemoattractant protein-1 (MCP-1) is a cytokine known to be involved in the recruitment of monocytes to the sites of inflammation [100]. MCP-1 activates the chemokine receptor 2 (CCR2), a seven-transmembrane helix GPCR implicated in inflammatory pain responses [101]. You and colleagues have recently shown that MCP-1 selectively inhibits Cav3.2, but not the Cav3.1 and Cav3.3 T-types [102]. Interestingly, this modulation does not require CCR2 receptor activation and seems to involve a direct action of the ligand on the channel. Whole-cell T-type currents in acutely dissociated DRG neurons are effectively inhibited by MCP-1, consistent with the notion that these cells predominantly express Cav3.2. The MCP-1-induced T-type channel response is eliminated by heat denaturation and further is sensitive to the application of the divalent metal ion chelator diethylenetriaminepentaacetic acid, which suggests that metal ions acts as a co-factor. Together, these findings may provide novel avenues for the development of inhibitors of T-type channels for the treatment of pain and other T-type channel linked disorders [102].

3.4. Endostatin

Our recent studies have shown that endostatin (ES), a carboxyl-terminal proteolytic fragment of collagen XVIII, selectively inhibits T-type currents in human glioblastoma U87 cells, where Cav3.1, Cav3.2 and Cav3.3 are all endogenously expressed [103]. Pretreatment with NNC 55-0396, a mibefradil nonhydrolyzable analog with reduced L-type Ca^{2+} channel affinity, completely abolishes the ES-induced T-type current inhibition. The inhibition is independent of either G-protein or protein tyrosine kinase. Examining heterologously expressed Cav3 subunits in HEK293 or CHO cells, Cav3.1 and Cav3.2, but not Cav3.3, were significantly inhibited by ES. The inhibition of T-type currents by ES is highly dependent upon the inactivation state of the channels. Interestingly, ES hyperpolarizing induces a hyperpolarizing shift in the steady-state inactivation profile in U87 cells, whereas the activation curve is not affected. Although it remains unclear whether the hyperpolarizing shift in steady-state inactivation produces a significant modification in the T-type window current, the results suggest that the reduced T-type currents by application of ES are due to more channels remaining in the inactivated state.

4. Regulation of T-type channels by modulation of their expression

The subcellular distribution of T-type channels across the central nervous system varies with T-type isoform and brain region [12,15,16]. For example, in neocortical pyramidal cells, Cav3.1 channels exhibit a mainly somatic distribution, whereas Cav3.3 channels are expressed at the soma, as well as in proximal and distal dendritic [12]. The molecular mechanisms that underlie the differential subcellular distribution and membrane trafficking of individual channel subtypes are unknown. For example, although co-expression of T-type α_1 subunits with HVA calcium channel β and $\alpha_2\delta$ subunits can increase α_1 subunit surface expression [104], no physical interaction among these subunits has ever been demonstrated. It is likely that different T-type channels are able to associate with a plethora of interacting proteins, which in turn might affect the extent of membrane trafficking, and the specific targeting to various subcellular loci. It is also important to note that increased Cav3.2 channel membrane expression has been reported for channels possessing missense mutations associated with childhood absence epilepsy [105], although it is unclear whether this is due to the altered ER retention or

increased membrane trafficking/stability. Direct effects of epilepsy mutations on membrane expression or effects on interactions with regulatory proteins that are involved in channel targeting could potentially account for their pathophysiological impact even in the absence of any alterations in channel biophysical properties.

Another potential mechanism for affecting the expression of T-type channels might be related to hormonal changes that occur in epilepsy patients [106]. For instance, it has been shown that 17β-estradiol treatment induces an increase in Cav3.1 mRNA expression, which leads to increased functional expression of Cav3.1 channels and increased burst-firing in hypothalamic neurons [107] and may at least in part account for the increased T-type expression observed in mouse models of absence epilepsy [108]. An up-regulation of T-type channel expression is also associated with both painful diabetic neuropathy [109] and irritable bowel syndrome (IBS) models [110] neuropathy in dorsal DRG sensory neurons. Conversely, knockdown of spinal Cav3.2 and Cav3.3 channels in rats mediates potent analgesia [111,112]. Although potentially directly contributing to pathophysiology, altered regulation of either trafficking of T-type channels to the plasma membrane, or affecting their stability in the plasma membrane, might provide a novel means of modulating T-type activity for therapeutic purposes.

T-type channel variant expression can further be regulated by alternate splicing [113,114]. Underscoring the significance of alternative splicing to disease pathophysiology, the splicing of T-type subunits can crucially affect how the channels respond functionally to a missense mutation associated with absence epilepsy [115] and further, splice variant expression can be altered during development and in certain disease models [116–118]. A recent study has provided evidence that certain mutations and/SNPs associated with childhood absence epilepsy might affect splicing of the Cav3.2 gene by altering splice junctions [119]. This is in turn predicted to give rise to inappropriate splice variants in specific cell types and result in altered neuronal function. Along these lines, when conducting *in vitro* mutagenesis studies, is essential that the mutations be introduced into the appropriate splice variant since effects of such mutations might manifest themselves only in certain channel variants [120]. Overall, alterations in the normal T-type expression patterns may play significant roles in T-type channel pathophysiology although our current understanding of the underlying molecular mechanisms that regulate T-type channel expression at the mRNA and protein levels remains poor.

5. New insights into the modulation of T-type channels

5.1. Modulation of T-types by muscarinic M1 receptors

Hildebrand and colleagues have shown that activation of muscarinic M1 receptors selectively inhibits transiently expressed Cav3.3 channels in HEK293 cells [121] (*see* Table 1 and Fig. 2). The authors showed that this inhibition is mediated by a $G_{q/11}$-linked pathway and partially involves $G_{\beta\gamma}$ subunits. The M1 receptor-mediated modulation appears not to involve any of the major second messenger pathways and suggest a novel regulatory pathway for T-type modulation. The M1-receptor mediated effect may involve a redundant inhibitory mechanism composed of $G_{\beta\gamma}$ and unidentified second messengers that complement each other. It is also possible that multiple kinases are activated by M1 receptors concomitantly, with each being capable of inhibiting T-type activity. Such a mechanism would be consistent with the authors' observation that multiple structural regions of the channel are involved [121].

5.2. Modulation of T-types by dopamine D1 receptors

Wolfe and colleagues have shown that inhibition of Cav3.2 channels by dopamine D1 receptors expressed in the adrenocarcinomal cell line H295R are mediated by direct interaction of $G_{\beta2\gamma2}$ subunits

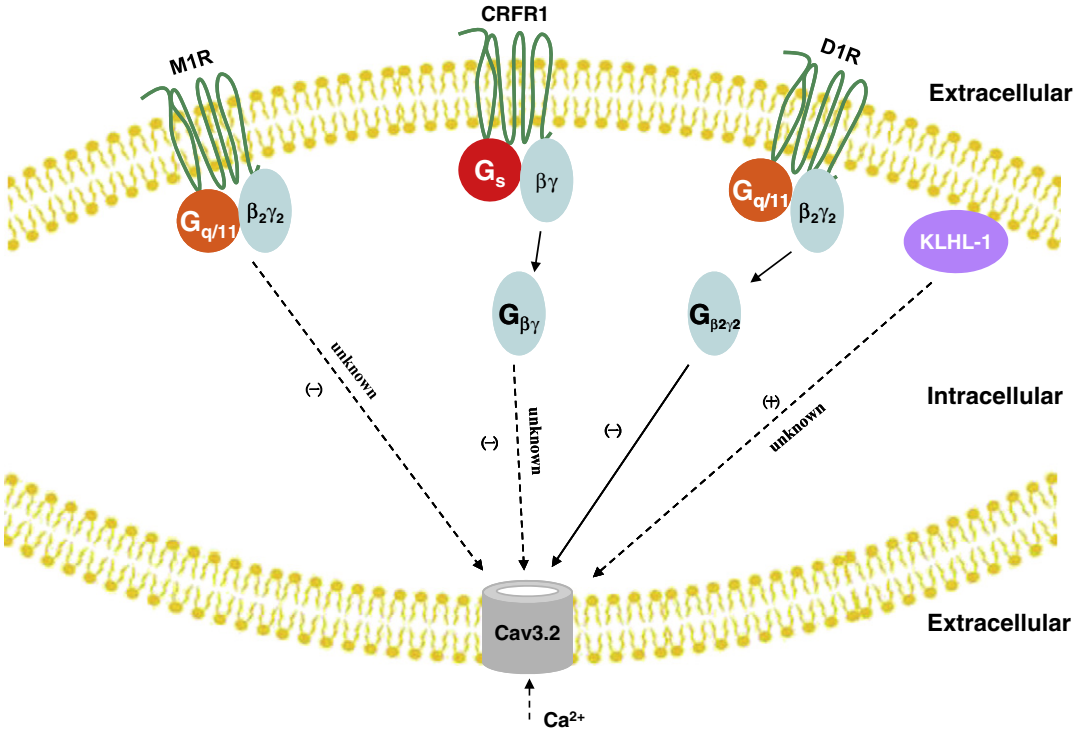

Fig. 2. New insights into the modulation of T-type channels. Muscarinic M1 receptor activation via $G_{q/11}$ inhibits T-type activity via an undefined mechanism pathway that does not involve the phospholipase Cβ (PLC_β)/PKC pathway and requires partial involvement of $G_{\beta\gamma}$ subunits. Activation of CRF1 receptors inhibits T-type channels via activation of $G_{\beta\gamma}$ subunits via a cholera-toxin-sensitive Gs subunit. The final coupling mechanism between these $G_{\beta\gamma}$ subunits and the T-type channel is not understood. D1 receptor activation via $G_{q/11}$ inhibits T-type activity via a direct action of $G_{\beta2\gamma2}$ subunits. The neuronal actin binding protein Kelch-like 1 (KLHL1) selectively increases Cav3.2 current density and deactivation kinetics. These changes lead to an overall increase in the Ca^{2+} influx without a change in conductance or open probability.

with Cav3.2 [39,122] (Table 1 and Fig. 2). $G\beta_2\gamma_2$ inhibits Cav3.2 channels directly without affecting the voltage-dependent gating properties, whereas other types of G-protein β subunits do not mediate this type of direct regulation. It is important to note that this form of regulation is specific to the $G_{\beta 2}$ subunit. Thus, a possible explanation for the observed differences in the signaling by these two $G_{q/11}$ protein-coupled receptors might be attributed to a low endogenous level of $G_{\beta 2\gamma 2}$ dimer in HEK293 cells. Recent studies from the Barrett lab have indicated that Cav3.2 must be phosphorylated by protein kinase A to be responsive to $G_{\beta 2\gamma 2}$ inhibition [122]. This leads to a scenario in which differences in basal phosphorylation states can alter hormone-mediated inhibition of Cav3.2 and adds yet another possible explanation for the variability observed across studies.

5.3. Modulation of T-types by CRFR1

The Soong group has described the regulation of Cav3.2 channels by corticotrophin releasing factor receptors (CRFR) [72] (Table 1 and Fig. 2). In transiently transfected HEK cells the activation of CRFR1 selectively inhibits Cav3.2 channels. The inhibition does not involve protein kinase pathways, but is dependent upon $G_{\beta\gamma}$ subunits activated via a cholera-toxin-sensitive G_α pathway. Interestingly, this observed modulation differs from the previously described inhibition mediated by $G_{\beta 2\gamma 2}$, in which a leftward shift in the half-inactivation potential was observed. Such a shift in the steady-state inactivation profile leads to a decrease in size of the window current and a reduced T-type availability for opening. However, a recent report by Kim and colleagues [123] has shown that activation of CRF receptors inhibits T-types expressed in MN9D cells (a cell line with characteristics of dopaminergic neurons), an effect is dependent on PKC activity. This suggests that not only the coupling between CRFR and T-type channels but also the consequence of PKC activation are highly dependent on the cellular environment, splice variant or other factor.

5.4. Modulation of T-types by KLHL1

Aromoralaran and colleagues have reported another novel regulatory mechanism in that the neuronal actin binding protein (ABP) Kelch-like 1 (KLHL1) selectively increases Cav3.2 current density and deactivation kinetics [124] (Fig. 2). These changes lead to an overall increase in Ca^{2+} influx, without altering the conductance or open probability. KLHL1 is a constitutive protein that is widespread in the brain and contributes to the modulation of pacemaker activities, short burst-firin, and low-threshold Ca^{2+} spikes [125]. KLHL1 also participates in neurite outgrowth and its genetic elimination in Purkinje neurons leads to dendritic atrophy and motor insufficiency.

6. Conclusions

T-type channels are critical contributors to membrane excitability in both neuronal and nonneuronal cells [126,127], and aberrant T-type function and expression have been linked to a number of serious disorders. Although there is an increasing understanding of the molecular determinants that underlie regulation of T-types by a range of second messenger pathways, the intricate mechanisms that control T-type expression and distribution remain largely unknown. Animals with the genetic knockout of Cav3.1 and Cav3.2 have been produced and will be helpful to further explore the involvement of T-type channel isoforms in a variety of physiological and pathophysiological states. To date, the Cav3.1 knockout mice have provided solid evidence that this T-type channel plays a major role in sleep and absence epilepsy by affecting burst-firing in the thalamocortical relay neurons [128,129] while the Cav3.2 knockout mice has confirmed a role for Cav3.2 in nociception [130]. As yet, there has been no report showing the functional consequences of Cav3.3 deficiency. Gene knockout mice are undoubtedly useful animal models to probe the physiological and pathophysiological roles of T-type channels. However, the constitutive inactivation of these genes may lead to compensatory responses that mask the precise involvement of T-type channel activity. For example, discrepancies in the neuropathic pain phenotype between Cav3.2 knockout mice and animals that undergo antisense knockdown [111,130] suggest that compensatory effects in knockout animals may in part alleviate responses to hyperalgesia. In some cases the effects of the changes to T-type activity may also be related to changes in potassium channel activity. Small- and large-conductance Ca^{2+} activated K^+ channels have been shown to be functionally coupled in neurons and vascular smooth muscle cells where they are involved in regulating neuronal firing patterns and vasodilation, respectively [131–133]. Recently, voltage-activated K^+ channels (Kv) [134,135] and Ca^{2+}-activated K^+ channels of intermediate conductance (KCa3.1) [136] have also been found to be coupled both functionally and physically to T-type channels.

From the clinical perspective, the search for subtype-specific T-type channel blockers has been of considerable interest. While a number of classes of T-type blockers have been described (dihydropyridines, succinimide derivatives, diphenylbutylpiperidine derivatives, bendodiazepines, anesthetics), their action has not yet proven sufficiently selective against the various T-type isoforms [137–141]. Given that T-type channels exhibit isoform-specific distributions and biophysical and modulatory properties, the need to design drugs selective for a given T-type variant is likely to be crucial yet significant challenge.

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