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Retinal TRP channels: Cell-type-specific regulators of retinal homeostasis and multimodal integration

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Abstract

Transient receptor potential (TRP) channels are a widely expressed family of 28 evolutionarily conserved cationic ion channels that operate as primary detectors of chemical and physical stimuli and secondary effectors of metabotropic and ionotropic receptors. In vertebrates, the channels are grouped into six related families: TRPC, TRPV, TRPM, TRPA, TRPML, and TRPP. As sensory transducers, TRP channels are ubiquitously expressed across the body and the CNS, mediating critical functions in mechanosensation, nociception, chemosensing, thermosensing, and phototransduction. This article surveys current knowledge about the expression and function of the TRP family in vertebrate retinas, which, while dedicated to transduction and transmission of visual information, are highly susceptible to non-visual stimuli. Every retinal cell expresses multiple TRP subunits, with recent evidence establishing their critical roles in paradigmatic aspects of vertebrate vision that include TRPM1-dependent transduction of ON bipolar signaling, TRPC6/7-mediated ganglion cell phototransduction, TRP/TRPL phototransduction in *Drosophila* and TRPV4-dependent osmoregulation, mechanotransduction, and regulation of inner and outer blood-retina barriers. TRP channels tune light-dependent and independent functions of retinal circuits by modulating the intracellular concentration of the 2nd messenger calcium, with emerging evidence implicating specific subunits in the pathogenesis of debilitating diseases such as glaucoma, ocular trauma, diabetic retinopathy, and ischemia. Elucidation of TRP channel involvement in retinal biology will yield rewards in terms of fundamental understanding of vertebrate vision and therapeutic targeting to treat diseases caused by channel dysfunction or over-activation.

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1. Introduction

The primary function of the vertebrate retina is to intercept photons, support the percolation of electro-chemical signals across specialized circuits composed of neurons and glia, and distribute retinal output to visual centers in the midbrain via transmission of action potentials in the optic nerve. The types of retinal cells, their organization, and communication with endothelial and pigment epithelial cells (RPE) that constitute the outer and inner blood-retina barriers are conserved from cyclostomes to mammals. At first approximation, the retina appears to be utterly devoted to processing light-evoked signaling downstream from photoreceptors (rods, cones and ipRGCs), Still, it is becoming increasingly evident that light-independent signals (mechanical stimuli, temperature, ionic composition, and the inflammatory milieu) profoundly influence retinal development, function, and pathology (Grüsser et al., 1989; Križaj et al., 2014; Križaj, 2019). The biomechanical milieu alone consists of an assortment of signals - mechanical loading from intraocular pressure (IOP), blinking, sneezing, eye rubbing, activity-dependent changes in ion gradients and shear forces within blood vessels – that may interact with light-evoked signals at every stage of retinal processing, but current literature leaves many gaps concerning our understanding of molecular mechanisms through which mechanical, ionic and inflammatory stimuli contribute to vision loss in diseases such as glaucoma, diabetic retinopathy, ischemia, and retinal detachment. This review shows that many types of retinal dysfunction involve pathological over- or underactivation of evolutionarily conserved sensory transducers within the light-independent signaling circuits. Functioning predominantly as conduits for the second messenger calcium, these ion channels – belonging to the transient receptor potential (TRP) channel family - mediate the cells' responsiveness to touch, temperature, osmolarity, taste, pheromones, acidity, pain, inflammation, oxidation, metabolic energy, and polyunsaturated fatty acids across the body. Transcriptomic analyses show that every retinal cell type expresses multiple TRP subunits, some of which may interact (Gilliam and Wensel, 2011; Choi et al., 2015; Jo et al., 2022).

The vertebrate TRP superfamily has been initially identified by homology with the TRP channel gene encoding a light-activated channel in *Drosophila* photoreceptors (Cosens and Manning, 1969; Wu et al., 2010; Montell et al., 2002). Gene sequencing revealed the family to be ancient, with many individual members traced to the Cnidaria-Bilateria junction more than half a billion years ago (Peng et al., 2015) (Fig. 1). All TRP channels have in common six transmembrane domains with a pore-forming loop in a hydrophobic stretch between transmembrane segment 5 and 6 (S5 and S6) and motifs that are conserved across some isoforms (e.g., ankyrin (ANK) repeats, proline-rich domains (PRD); coiled-coil domains; and the TRP-box) (Clapham, 2003). In humans, the superfamily encompasses six families with 27 members: Canonical (TRPC1-7), Vanilloid (TRPV1-6), Melastatin (TRPM1-8), Ankyrin (TRPA1), polycystin (TRPP1-3) and Mucolipin (TRPML1-3). The canonical family was identified first, with the founding member TRPC1 as the homolog of TRP. The remaining subfamilies are named following the original designation of the first family member. Thus, the vanilloid family tracks TRPV1, identified initially through expression cloning for a channel activated by vanilloid compounds such as capsaicin, and the melastatin family tracks TRPM1, a putative tumor suppression protein (Montell et

al., 2002). While the majority of TRP proteins function as non-selective cation channels with isoform-specific calcium vs. sodium permeability (P_{Ca}/P_{Na} ~10), TRPV5, TRPV6, and TRPM3α2 function as Ca^{2+}–selective channels and TRPM4, TRPM5 and TRPM3α1 function as monovalent cation (mainly Na^{+}) channels. The C–terminal domains of TRPC and TRPV channels have binding sites for Ca^{2+} and Ca^{2+}–regulated proteins and are therefore susceptible to modulation by changes in Ca^{2+} induced by other cell receptors and channels. The cytoplasmic domains of TRP channels recruit large complexes of proteins, lipids, and small molecules into macromolecular complexes. Nearly all TRP families have potential mechanosensory members, with most isoforms responding to mechanical stimuli in a context– and cell-type-dependent manner.

A primary functional role for TRP channels is as a conduit for Ca^{2+}, a key 2nd messenger that regulates many cellular signaling mechanisms. Due to their voltage independence, TRP channels subserve Ca^{2+} influx and control the membrane potential in resting excitable and non-excitable cells. Background Ca^{2+} entry mediated by TRP channels modulates voltage-operated signaling, neurite outgrowth, hormone secretion, and contraction in neurons and myocytes, whereas ‘non-excitable cells’ utilize TRP channels as a major source of calcium-based excitation that regulates gliotransmitter release, vascular tone, cell volume, Mg^{2+} reabsorption, contractility, fibrosis, and many other functions. TRP isoforms may function in receptor-operated, store-operated, and/or stretch-operated modes and adopt multiple activation mechanisms via association with G protein-coupled receptors (GPCRs), growth factor receptors (e.g., ET-1), protease-activated receptors, the STIM1 complex and the cytoskeleton (Moran et al., 2011; Nilius and Szallasi, 2014). Some TRP channels (TRPV1, TRPM8, TRPP, TRPML) operate in the plasma membrane and as Ca^{2+} release channels from intracellular organelles (lysosomes, ER, Golgi apparatus, and mitochondria) (Gees et al., 2014). While detailed analyses of TRP signaling in the retina are relatively sparse, investigations in heart, lung, brain, vasculature, immune system, bone, and gut used global KOs, floxed mice, and selective shRNA/pharmacological modulators to document a wide range of sensory functions that include mechanosensation, thermosensation, phototransduction, chemosensation and nociception (Clapham, 2003; Nilius and Szallasi, 2014; White et al., 2016; Križaj, 2020). In recognition of the fundamental importance of TRP signaling, the Nobel Prize Committee awarded the 2021 Medicine Prize to University of California San Francisco’s David Julius for the pioneering work on heat-sensitive “capsaicin receptors” (TRPV1) TRPV2 and TRPM8 channels.

Mammalian retinas express most if not all TRP isoforms. Northern blots in the paper by Gilliam and Wensel (2011), the first to conduct a systematic analysis of retinal TRP expression, showed the highest signals for TRPM1, TRPM3, TRPV4, TRPP2 > TRPC2, TRPC6, TRPM2, TRPM4, TRPM7, TRPML1, TRPV1, TRPV2, and relatively weak expression of TRPM6, TRPV5, TRPV6, and TRPA1. Retinal neurons, glia, epithelial and endothelial cells express cell type-specific subunits (e.g., TRPM1 in bipolar neurons), whereas other subunits (notably, TRPC channels) show broad expression across all layers (Gilliam and Wensel, 2011; Molnar et al., 2012). Mutation studies revealed that TRP signaling plays fundamental and irreplaceable functions in vertebrate vision: TRPM1 mutations cause congenital stationary night blindness type 2 in mice, horses, and humans (Koike et al., 2010a); TRPML mutations, photoreceptor degeneration (Sun et al., 2000);

TRPV4 mutations, retinal degeneration (Thibodeau et al., 2017) while TRPM3 mutations were associated with early-onset cataracts and primary open angle glaucoma (Bennett et al., 2014). In general, however, our understanding of retinal TRP signaling lags far behind the body of work on other organs. Despite the ubiquitous expression, we do not know the identity of physiological inputs, modulatory mechanisms, and roles in pathology for the large majority of TRP subunits, and the pool of existing data includes studies with conflicting results. The absence of information about TRP channel signaling in vertebrate retinas contrasts sharply with the in-depth characterization of dTRP channel expression and function in *Drosophila* phototransduction. It is clear that TRP channels equip retinal cells – neurons and non-excitable cells alike - with the capacity to integrate light-activated signals with many types of mechanical stimulus (strain, shear, compression, swelling), endogenous and extracellular chemical agents, toxic compounds and/or temperature. Because many if not most cell types in the vertebrate retina express multiple TRP isoforms, polysensory integration of light-induced and light-independent signals is likely to take place at every stage of retinal processing.

2. TRP signaling in Müller glia

Müller cells constitute ~90% of the retinal glial population with crucial functions in trafficking, release/recycling of neurotransmitters, synaptogenesis, water transport, immune signaling, retinal (lactate, glucose, and glutamine) metabolism, vascular function, and K^+ siphoning (Bringmann et al., 2006; MacDonald et al., 2015; Vecino et al., 2016; Musada et al., 2020). Their ovoid cell body emanates two processes towards the OLM and the ILM (Fig. 2A and B), with lateral offshoots that tile the OPL and IPL, ensheath retinal neurons, contact microglia and blood vessels, and fasciculate optic nerve head axons. The apical process connects to photoreceptor inner segments with adherens and tight junctions to form the outer limiting membrane (OLM), whereas endfeet contacts with endothelial cells and astrocytes contribute to the inner limiting membrane (ILM) and the inner blood-retina barrier (Wang et al., 2017; Reichenbach and Bringmann, 2010; Shen et al., 2012). Müller cells can therefore be visualized as nonoverlapping columnar units that control signaling, metabolism, and viability of all neurons while constituting a functional link between retinal, vitreal, and subretinal spaces. In addition to being ideally positioned to regulate mechanical, metabolic, and chemomodulatory signaling under homeostatic and pathological conditions, this radial glia are amongst the first retinal cells to respond to environmental, genetic, and signaling stressors. The reactive response of Müller glia is characterized by hypertrophy and release of gliotransmitters and cytokines (Reichenbach and Bringmann, 2010; Vecino et al., 2016), with cells in some species exhibiting a remarkable potential for proliferation, pluripotency, and neurogenic programming (Lahne et al., 2020).

2.1. TRP channels and calcium signaling in Müller glia

Müller cells in many species are not electrically excitable due to minimal expression of voltage-gated channels and Ca^{2+}-permeable glutamate receptors but nonetheless exhibit excitability via spontaneous and activity-dependent activation of voltage-independent Ca^{2+}-permeable channels and Ca^{2+} release from internal compartments (Keirstead and Miller, 1995; Huang et al., 2011; Grosche et al., 2016). Cytosolic Ca^{2+} signals often occur as waves

that regulate the biology of adjacent neurons, endothelial cells, pericytes, microglia, and astrocytes via the release of gliotransmitters (glutamate, D-serine, and ATP/adenosine) and cytokines (TNFα, MCP-1, IL-1β) (Newman and Zahs, 1998; Metea and Newman, 2006a; Kurth-Nelson et al., 2009; Yarishkin et al., 2018a; Tworig et al., 2021). Ca^{2+} waves can be initiated by TRP channels, Orai channels, and purinergic P2X receptors and amplified by the substantial driving force from the hyperpolarized (~−90 to − 120 mV) membrane potential. Presently the most studied TRP subunit in Müller glia is TRPV4, with expression documented for mouse (Ryskamp et al., 2014a; Jo et al., 2015), rat (Sappington et al., 2015), pig (Taylor et al., 2017), non-human primate (Gao et al., 2019) and human (Ryskamp et al., 2011) preparations. TRPC1, TRPV4, and TRPC6 subunits have been linked to CICR and SOCE, and TRPC1 and TRPV4 were implicated in the propagation of Ca^{2+} waves, Ca^{2+}-dependent release of gliotransmitters, cytokines, eicosanoids, as well as regulation of the blood-retina barrier (Phuong et al., 2016; Thébault, 2021). mRNA/antibody analyses additionally documented Müller cell expression of TRPA1, TRPV2, TRPV6, TRPM3 and TRPP1 subunits (Ryskamp et al., 2014b; Jo et al., 2015, 2022; Križaj, 2019; Souza Monteiro de Araújo et al., 2020) which remain to be investigated functionally. Immortalized cell lines such as QMMuC1 may differ from native cells with respect to TRP signaling during tonic and evoked activity and TRP channel coupling to downstream signaling pathways.

2.2. TRPV4 and TRPC1-dependent mechanosensing in Müller glia

Müller glia continuously experience tensile stretch, tugging, and changes in cell volume (Fortune, 2019). The cells also provide mechanical support to the retina (MacDonald et al., 2015) and are exquisitely sensitive to every type of mechanical stress. Experimental stretch is a powerful regulator of Müller cell gene expression (Wang et al., 2013) and retinal detachment, intraocular pressure, and indentation were shown to evoke inward currents and $[Ca^{2+}]_i$ increases that were linked to gliotransmitter/cytokine release and reactive gliosis (Puro 1991; Woldemussie et al., 2004; Lindqvist et al., 2010; Agte et al., 2017; Matsumoto et al., 2018). Extracellular matrix (ECM) stretch evokes dose-dependent $[Ca^{2+}]_i$ elevations that are partially suppressed by pharmacological inhibition of TRPV4 and TRPC1 channels and by ablation of *Trpv4* and *Trpc1* genes (Jo et al., 2022). TRPV4 agonists mimic, and antagonists inhibit, mechanically evoked calcium signals (Ryskamp et al., 2014a; Jo et al., 2022). TRPV4$^{-/-}$ Müller cells show reduced sensitivity to stretch, swelling, and detachment and reduced sensitivity to chronic ocular hypertension (Ryskamp et al., 2014a). Similar to mouse Müller cells, their guinea pig counterparts respond to mechanical poking with $[Ca^{2+}]_i$ responses that are insensitive to the Piezo1 channel blocker GsMTx4 (Agte et al., 2017); they have not yet been tested for TRPV4. ~35% reduction in the amplitude of calcium responses induced by moderate (~6%) ECM strains was reported in TRPC1$^{-/-}$ Müller cells (Jo et al., 2022). Because stretch-induced signals in TRPV4$^{-/-}$ Müller glia are unaffected by TRPC1 antagonists, and responses in TRPC1$^{-/-}$ cells are suppressed by TRPV4 blockers (Jo et al., 2022), TRPV4 homotetramers may co-exist with TRPC1-TRPV4 heteromers (Greenberg et al., 2019; Cullimore et al., 2022). The precise sequence of mechanical-biophysical events that link membrane stress to Müller glial TRP activity remains to be elucidated, with possibilities including gating by lipid bilayer distension/curvature, integrin tethering, ECM deflection, and/or activation via stretch-sensitive PLA2 and STIM1 proteins (Ryskamp et al., 2014a; White et al., 2016; Servin Vences et al., 2017;

Potla et al., 2020). IOP-induced gliosis is decreased in TRPV4$^{-/-}$ retinas but augmented in TRPC1/3$^{-/-}$ retinas (Ryskamp et al., 2014a; Molnar et al., 2016), suggesting that TRPV4 and TRPC1-containing channels stimulate different downstream signaling pathways.

Given that both overactivation and underactivation of TRPV4 signaling in Müller cells induce reactive gliosis, we propose that the channel participates in homeostatic maintenance and inflammatory activation. Another exciting aspect of TRPV4 signaling is polymodal additivity that can be unmasked by facilitation of the cells' pressure response by body temperature (Matsumoto et al., 2018) and by combining its activation by swelling with exposure to chemical agonists (Toft-Bertelsen et al., 2017). Polymodality of gating probably reflects signal integration at different molecular domains (Vriens et al., 2004; Garcia-Elias et al., 2008).

Mechanosignaling in Müller cells bears similarities to brain astrocytes, which respond to indentation and pressure with TRPV4 and TRPC1-dependent Ca^{2+} influx, ATP, and glutamate release. TRP-dependent gliotransmitter release might help synchronize local neuronal and microglial activity (Malarkey et al., 2008; Diaz et al., 2019; Shibasaki, 2020; Turovsky et al., 2020). The retina is an ideal preparation to investigate such processes: in contrast to 20–30% of the brain astrocyte population that expresses TRPV4 (Shibasaki et al., 2014; Pivonkova et al., 2018), all retinal Müller cells manifest robust TRPV4-ir and functional responsiveness (Ryskamp et al., 2014a, 2015; Jo et al., 2015). It should also be noted that TRP channels usually collaborate with other mechanosensitive channels (such as Piezo and tandem-pore potassium families) and that cellular mechano-homeostasis requires synergistic activation of transducers with opposing effects on intracellular signaling (Yarishkin et al., 2019, 2021).

2.3. Osmoregulation in Müller glia reflects dynamic communication between TRP and AQP channels

Retinal osmolyte and water content are continuously monitored and regulated by the inner and outer retina-blood barriers constituted by Müller glia and RPE, respectively. Changes in osmolarity deform the cell membrane via swelling or shrinking, which in turn may affect many membrane-delimited processes and contribute to mechanosensation. Over the past several decades, many studies highlighted the multifaceted contributions of Müller cells to redistribution of ions and water between the retina, vitreous, and subretinal spaces (reviewed in Reichenbach and Bringmann, 2010). Given their central role in osmoregulation, it stands to reason that Müller glia sense changes in cell volume, with TRPV4 - a nonselective cation channel that was identified based on its sensitivity to swelling (Strotmann et al., 2000) and subsequently implicated in systemic and cellular osmotransduction (White et al., 2016) - at its nexus. The cells indeed strongly react with TRPV4 antibodies. By far the strongest TRPV4-ir was detected in the endfoot compartment (Jo et al., 2015; Ryskamp et al., 2014a; Li et al., 2021a,b) where proximity to AQP4, ER, and mitochondrial compartments subserves interactions with CICR, SOCE, K^+ and water transport (Fig. 2B, E). Antibody labeling is punctate, presumably due to TRPV4 aggregation into macromolecular complexes that may include aquaporins, PACSIN 3, actin, microtubules, phosphatidylinositol biphosphate (PIP2), IP3 receptors, TRPM4 and

anoctamin channels (e.g., Garcia-Elias et al., 2008; Jo et al., 2015; White et al., 2016; Redmon et al., 2017).

Wild-type Müller cells respond to synthetic TRPV4 agonists (GSK1016790A and 4α-PDD) and the endogenous agonist arachidonic acid with a nonselective cationic conductance that reverses at 0 mV (Ryskamp et al., 2014a, 2015; Toft-Bertelsen et al., 2019). In contrast to moderate outward rectification, typical of "generic" TRPV4-mediated currents (Watanabe et al., 2003), TRPV4 currents evoked by agonists and swelling in Müller glia exhibit a linear I-V relationship (Lapajne et al., 2022). The onset of the TRPV4-mediated current and the attendant increase in $[Ca^{2+}]_i$ are slow (~minutes; Fig. 2C) due to obligatory activation of a polyunsaturated fatty acid messenger cascade downstream from phospholipase A2 (PLA2) (Fig. 2D). PLA2 is a Ca^{2+}- and stretch-dependent enzyme that cleaves endocannabinoids to produce arachidonic acid, which in turn is metabolized by cytochrome P450 (CYP450) and epoxygenases into epoxyeicosatrienoic acids (5′6′-EET, 8′9′-EET, and 11′12′ EET) that function as final common activators of TRPV4 (Berna-Erro et al., 2017; Watanabe et al., 2003). The PLA2-EET cascade amplifies the original stimulus (Ca^{2+} influx across the channel pore), thereby equipping the glia with an extraordinary sensitivity to mechanical, thermal, lipid, and osmotic inputs (Matsumoto et al., 2018; Toft-Bertelsen et al., 2019; Redmon et al., 2021).

As in astrocytes and *ex vivo* brain tissue (Križaj et al., 1996; Risher et al., 2009), the volume of Müller cells is roughly proportional to the tonicity of the extracellular milieu (Jo et al., 2015). The cells swell in response to a reduction in extracellular tonicity or under the condition of energy depletion, which produces cytotoxic edema of Müller cell processes due to net ion and water entry into the retina. Swelling is associated with an increase in cytosolic $[Ca^{2+}]_i$ that is sensitive to TRPV4 antagonists and *Trpv4* gene deletion. TRPV4 inhibition obliterates calcium signals induced by weak (~5–15 mOsm) stimuli and suppresses 40–70% of the calcium response evoked by large (120–190 mOsm) hypotonic gradients. Regulatory volume decrease (RVD) observed when cells are exposed to large hypotonic gradients, is inhibited by BAPTA, and missing in $TRPV4^{-/-}$ cells (Jo et al., 2015; Toft-Bertelsen et al., 2019). Although Müller cell volume regulation shows strong Ca^{2+}-dependence, osmosensitivity of the RVD response may be too low to play significant roles under physiological circumstances. In cell-based assays, hypotonicity activated TRPV4 channels via tyrosine phosphorylation at the N-terminus, PLA2 activation, and generation of lipid metabolites (Vriens et al., 2004; White et al., 2016). Another critical factor is the rate of lipid distension that works together with PLA2 activation to control the extent of channel activation (Ryskamp et al., 2014a; Toft-Bertelsen et al., 2017). The rate of cell swelling is governed by the density, location, and hydraulic permeability of AQP4 channels (Jo et al., 2015; Toft-Bertelsen and Macaulay, 2021), with deletion of *Aqp* genes slowing TRPV4 activation by reducing the rate of water influx and membrane expansion (Liu et al., 2006; Jo et al., 2015; Toft-Bertelsen et al., 2017). The latter involves PLA2-dependence of TRPV4 activation and activation of the eicosanoid cascade. Despite the instantaneous osmotic equilibration mediated by AQPs, the onset of Ca^{2+} signaling in hypotonically challenged cells is likely to reflect the time course of PLA2-EET signaling. We do not yet know whether AQP4 forms a macromolecular complex with TRPV4 (as proposed for cortical astrocytes; Benfenati et al., 2011) and cPLA2, whether AQP4 surface localization involves

Ca^{2+}/CaM-dependent step downstream from TRPV4 (Kitchen et al., 2020) and/or whether AQP4 controls the TRPV4 pore indirectly through expansion of the plasma membrane (Mola et al., 2021; Toft-Bertelsen et al., 2017).

Current evidence implicates Ca^{2+} influx through TRP channels in AQP-dependent swelling and RVD, with likely additional involvement of channel trafficking and activation of Ca^{2+}-dependent K^+ and Cl^- channels. TRPV4 agonists such as GSK1016790A and arachidonic acid facilitate swelling, whereas calcium chelation and *Trpv4* gene ablation reduce its rate and extent (Pannicke et al., 2006; Ryskamp et al., 2014a; Jo et al., 2015). AQP4 trafficking may be regulated by calcium-dependent and independent steps (Sidhaye et al., 2006). The positive feedback loop involving AQP-dependent swelling, TRPV4 activation, and Ca^{2+} influx may be exacerbated by the swelling-induced release of the agonist arachidonic acid (Pannicke et al., 2006; Reichenbach et al., 2007) to contribute to edema formation and breakdown of inner and outer blood-retina barriers in diabetic retinas (Arredondo Zamarippa et al., 2017; Orduna Rios et al., 2019). Within this context, AQP4-dependent swelling functions as a driver of retinal edema (e.g., Manley et al., 2000; Thrane et al., 2011). Conversely, chelation of intracellular calcium, PLA2 blockade, or deletion of the TRPV4 gene reduced the excessive influx of calcium into Müller cell processes, suppressed swelling (Ryskamp et al., 2014a; Jo et al., 2015; Pannicke et al., 2006) and ameliorated the reactive response to diabetes (Acharya et al., 2017). TRPV4 inhibition has been similarly effective in counteracting edema in the retina, brain, lung, and other tissues (Balakrishna et al., 2014; Hoshi et al., 2018; Orduna Rios et al., 2019; Chmelova et al., 2019; Haywood et al., 2022; Michinaga et al., 2021), suggesting that targeting TRPV4 channels might constitute an alternative anti-edema strategy to AQP4 downregulation/inhibition (Manley et al., 2000; Da and Verkman, 2004; Kitchen et al., 2020). In an additional benefit, this strategy might preserve homeostatic ion/water fluxes through the retinal glymphatic pathway.

In contrast to wild-type cells in which TRPV4 functions to sense and mediate swelling-evoked $[Ca^{2+}]_i$ signals (Ryskamp et al., 2014a; Iuso and Križaj, 2016), hypotonicity-induced Ca^{2+} increases in immortalized Müller cells do not involve TRPV4 activity (Netti et al., 2017).

2.4. TRPC1, store-operated calcium entry (SOCE), and calcium-induced calcium release (CICR)

Glial excitability is organized around communication between the plasma membrane and release channels in the endoplasmic reticulum (ER). Müller glia express ryanodine and inositol triphosphate receptors that are coupled to metabotropic receptor pathways and TRP channels (Keirstead and Miller, 1995; Da Silva et al., 2008; Lipp et al., 2009; Huang et al., 2010) (Fig. 3). The central CICR/SOCE hub is at the endfoot due to its packing with smooth ER, and extensive network of flat subplasmalemmal cisternae (Fig. 3D). $[Ca^{2+}]_i$ signals evoked by the TRPV4 agonist GSK1016790A are reduced ~40% in the presence of CICR blockers such as thapsigargin (Ryskamp et al., 2014a). TRP subunits are thus functionally coupled to ER Ca^{2+} release, phospholipase C (PLC) signaling and store-operated Ca^{2+} entry (SOCE) (Figs. 2D and 3D).

Store release-dependent excitability requires ER refilling with Ca^{2+} through store-operated Ca^{2+} entry (SOCE) – a cellular pathway through which plasma membrane cation channels are activated by the STIM1 (Stromal interaction molecule 1) ER depletion sensor. Müller cell SOCE is associated with a slowly developing inward cationic current that reverses at 0 mV (Fig. 3A and C), is accompanied by a rise in $[Ca^{2+}]_{i,}$ and often takes the form of Ca^{2+} waves that propagate from the endfoot towards the soma (Molnar et al., 2016; Phuong et al., 2016) (Fig. 3B). The depletion-induced current is ~50% suppressed by pharmacological inhibition of TRPC1 or deletion of the *Trpc1* gene (Fig. 3C), with the other component mediated by Orai channels (Molnar et al., 2016). *In situ* hybridization and transcript analyses corroborated strong *Trpc1* expression in the INL and purified Müller cells (Da Silva et al., 2008; Gilliam and Wensel, 2011; Molnar et al., 2012; Jo et al., 2022).

TRPC1 homotetramers cannot form a functional pore. Like heteromerization between *Drosophila* TRP and TRPL channels (Hardie, 2014; Katz and Minke, 2018), vertebrate TRPC1 subunits form obligatory heteromeric associations with canonical associations, vanilloid, or polycystin subunits. I-V properties of the TRPC1-containing channel pore in Müller cells (Fig. 3C) resemble the currents mediated by heteromeric TRPC1:V4 channels (e.g., Ma et al., 2011; Du et al., 2014). Indeed, $TRPC1^{-/-}$ and $TRPV4^{-/-}$ cells show reduced responsiveness to mechanical stimuli. Because TRPC1 subunits are also sensitive to stretch (Jo et al., 2022), they may serve as excitability conduits between mechanical stimuli, intracellularly stored calcium, and calcium signaling that combines mechanical stimulation, metabotropic receptors, CICR, PLC-dependent activation of TRPC3/6 channels, and SOCE (Fig. 3D).

Kelly and coworkers suggested that store-operated signaling in Müller glia involves TRPC6 channels (Da Silva et al., 2008), which belong to the diacylglycerol (DAG)-sensitive group of canonical TRP channels (together with TRPC3 and TRPC7 isoforms). Purified mouse Müller cell preparations express *Trpc1* and *Trpc6* transcripts (Da Silva et al., 2008; Jo et al., 2022) and their $[Ca^{2+}]_i$ response to DAG analogs (Fig. 2F) confirms functional expression of the TRPC3/6/7 subfamily. Interestingly, DAG is converted by lipases into arachidonic acid and metabolized into epoxygenase-derived eicosanoids (EETs), hydroxyeicosatetraenoic acids (HETEs), and leukotrienes that activate multiple vanilloid TRP isoforms. Hence, lipid signaling likely modulates multiple glial TRP subunits in series and in parallel.

2.5. Inflammation and disease

One of the earliest retinal responses to injury and stress is reactive gliosis that precedes neuronal phenotypes in glaucoma and diabetes and exacerbates neuronal injury from elevated IOP, neovascularization, BRB breakdown, and cytokine/chemokine release (Woldemussie et al., 2004; Inman and Horner, 2007; Devoldere et al., 2019). Müller glia respond to retinal detachment, intraocular pressure, and mechanical trauma with upregulation of glial fibrillary acidic protein (GFAP), vimentin, and complement proteins (Reichenbach and Bringmann, 2010). While retinal development and function appear unaffected in global TRPC1, TRPC3, TRPC6, and TRPA1 knockout mice (Molnar et al., 2012, 2016; Yarishkin et al., 2018a; Araújo et al., 2020), a range of structural and functional phenotypes emerges when the tissue is pushed out of homeostatic range. For example,

reactive gliosis evoked by intravitreal injection of TRPV4 agonists simulates the effects of mechanical/thermal stress (Ryskamp et al., 2014a), possibly due to activation of the JAK2/STAT3/NFkB pathway (Li et al., 2021a,b). Conditional TRPV4 ablation protects neurons from detachment-induced reactivity and inflammation by reducing the sensitivity of Müller cells to swelling, detachment, and temperature (Matsumoto et al., 2018). The cells were suggested to regulate inflammation angiogenesis via MCP-1, IL-1β, IL-6, VEGF-A, and TNFα cytokines (Almasieh et al., 2012; Vecino et al., 2016; Devoldere et al., 2019), with TRPV4 antagonists and gene deletion inhibiting swelling-induced cytokine release (Matsumoto et al., 2018). As noted above, reactive gliosis in normotensive retinas can be triggered by TRPV4 overactivation or by ablating TRPV4 channels (Ryskamp et al., 2014a). Thus, tonic TRP signaling is required to maintain a healthy homeostatic state, and inflammatory activation can follow under- and overactivation of homeostatic sensing.

A *Trpc1* SNP (rs7638459) was identified as a risk factor for type 2 diabetes (Chen et al., 2013), yet diabetic (STZ-treated) TRPC1/4/5/6 quadruple KO retinas showed protection against neuronal/pericyte loss (Sachdeva et al., 2018). In contrast to the proinflammatory effects of TRPV4 stimulation, TRPC1/3$^{-/-}$ retinas exposed to chronic ocular hypertension upregulate gliotic markers (Molnar et al., 2016), suggesting that TRPC1/3 activity helps maintain an anti-inflammatory state in the presence of chronic mechanical stress.

2.6. TRPV4 and lipid modulation

TRP channels tend to be very sensitive to membrane cholesterol, responding to depletion and supplementation with isoform-specific up/downregulation (Levitan and Barrantes, 2012; Lakk et al., 2021). Müller glia are the leading retinal producer and supplier of cholesterol which constitutes ~98% of total sterols in the retina, is required for glia-dependent synapse formation, and has been linked to acquired and inherited retinal degenerations such as Smith-Lemli-Opitz Syndrome, Niemann-Pick type C disease, diabetic retinopathy, macular degeneration (Fliesler and Bretillon, 2010) as well as glaucoma (Marcus et al., 2012). Retinas from animals with altered cholesterol levels and diabetes (Trivino et al., 2006) exhibit deficits - reactivity, hypertrophy, pathological swelling of Müller cells, and altered permeability of the microvascular endothelial barrier – that resemble the effects of excessive TRPV4 activation (Jo et al., 2015; Phuong et al., 2016; Ryskamp et al., 2014a; 2016). It would be interesting to explore whether ameliorating the reactive Müller glial response to hypercholesterolemia by PLA2 blockers (Acharya et al., 2017) includes suppressive or modulatory effects on TRPV4 activation (Ryskamp et al., 2014a) and whether channel activation is impacted by statins. Consistent with the multi-domain model of TRPV4 activation (Vriens et al., 2004), depleting free membrane cholesterol with scavenger cyclodextrins reduced the amplitude of agonist-, swelling, and temperature-evoked TRPV4 signals - effects that were reversed by cholesterol supplementation (Lakk et al., 2017). In contrast to endothelial cells (Saliez et al., 2008) but like trabecular meshwork cells (Lakk et al., 2017, 2021), TRPV4 in Müller glia does not partition into cholesterol-enriched lipid rafts and caveolar domains and thus the mechanism of its cholesterol sensitivity remains to be ascertained. It is possible if not likely that the channel is modulated by annular lipids that form hydrophobic pockets around the pore, by phosphatidylinositol-4,5-biphosphate (PIP2), and through cholesterol binding to Cholesterol Recognition/Interaction Amino acid

Consensus (CRAC/CARC) domains that span the loop between TM4 and TM5 of TRPV4 (Kumari et al., 2015).

2.7. Müller cells, endothelial cells, and the blood-retina barrier (BRB)

The inner blood-retina barrier consists of a tight non-fenestrated endothelial monolayer that maintains ionic and water homeostasis across the retina-vitreous space and is regulated by interactions between the endothelium, Müller cells, pericytes, ganglion cells, and astrocytes. The interdependence of signaling between these cell types is critical for BRB integrity, with TRPV4 channels expressed on multiple sides of the neurovascular junction. A detailed review of TRP-dependent modulation of endothelial function and blood flow is beyond the scope of this review, but the reader is directed to recent summaries (Thébault, 2021; Lapajne et al., 2022). Release of gliotransmitters, arachidonic acid, nitric oxide and eicosanoids from Müller endfeet may result in vasoconstriction or vasodilation (Newman, 2015; Someya et al., 2019), with the epoxygenase pathway upstream from TRPV4 gating functioning as a potent blood vessel dilator (Metea and Newman, 2006b; Hu et al., 2004) that may affect local hyperemia. The sensitivity of endothelial cells to TRPV4 agonists appears to be ~25-fold higher relative to Müller glial endfeet (Phuong et al., 2017; Jo et al., 2015), suggesting that blood vessels are highly attuned to changes in local osmotic and mechanical gradients. Overactivation of microvascular endothelial channels was associated with loss of barrier permeability (Phuong et al., 2016). Involvement of TRPV4 channels in diabetic pathology remains to be studied further, as high glucose-treated endothelial cells and cells studied in streptozotocin-induced rats show reduced TRPV4 expression (Monaghan et al., 2015) yet TRPV4 antagonists and channel ablation were reported to be protective in diabetic animals (Arredondo Zamarippa et al., 2019; Orduña Ríos et al., 2019). Cappelli et al. (2021) showed that ablation of TRPV4 channels increases pathological angiogenesis and reduces pericyte coverage without impacting normal postnatal development. Another layer of complexity may involve cell type- or context-dependent interactions between TRPV4 channels and resident TRPV1, TRPV2, TRPC3 and TRPC6 isoforms (Sachdeva et al., 2018; O'Leary et al., 2019; Guarino et al., 2020). Finally, the glymphatic paravascular compartment between the endfeet and the endothelium may constitute a TRPV4- and AQP4-dependent venue for rapid fluid exchange. An analogy with brain astrocytes (Butenko et al., 2012; Diaz et al., 2019; Turovsky et al., 2020) implicates TRPV4-dependent signaling in Müller glial endfeet in the modulation of intravascular pressure, neurovascular coupling, functional hyperemia and barrier permeability and retinal pathophysiology. Consistent with this, isolated and intact microvascular retinal endothelial cells respond to TRPV4-mediated Ca^{2+} influx with dissolution of adherens/occludens junctions, loss of barrier integrity and blood leakage that is restored by genetic and pharmacological suppression of TRPV4 activity (Phuong et al., 2016) in which $TRPV4^{-/-}$ retinas are protected against diabetes-induced edema and BRB breakdown (Orduna Rios et al., 2019). Another essential aspect of gliovascular signaling involves endothelial TRPV1, TRPV2 and TRPV4 channels that modulate angiogenesis, myogenic constriction, cell migration and neurovascular coupling (O'Leary et al., 2019; Monaghan et al., 2015; Barabas et al., 2020).

TRPC6 may be upregulated in Müller cells from hyperglycemic STZ-treated retinas (Sachdeva et al., 2018). RNAi-mediated *Trpc6* knockdown suppressed VEGF secretion and

abolished glucose- and calcium-dependent decreases in glutamate uptake in an immortalized cell line (rMC-1; Ma et al., 2020), suggesting potential functions at the neurovascular junction.

2.8. Other TRP subunits in Müller glia

TRPV1.—TRPV1 antibodies labeled Müller cells in mouse, rabbit (Martínez-García et al., 2013), and vervet monkey (Bouskila et al., 2020) but not rat (Leonelli et al., 2009) retinas. Transgenic TRPV1Cre:Ai9 and TRPV1Cre:Ai3 retinas show fluorescent TRPV1 reporter tags in a subpopulation of Müller cells (Lakk et al., 2018). Non-uniform expression of TRPV1 lineage markers in transgenic retinas could reflect differential expression of the reporter transgene or actual differences in regional *Trpv1* expression. It is worth noting that Müller cells represent a major retinal site for anandamide (AEA) uptake and degradation by fatty acid amide hydrolases (Glaser et al., 2005). Activity-dependent AEA release also modulates Müller glial TRPV1 signaling (Ryskamp et al., 2014b; M. Lakk and DK, unpublished observations). Comparison to other tissues (Alessandri-Haber et al., 2009; Balakrishna et al., 2014; Nilius and Szallasi, 2014) suggests potential roles in inflammatory and neuropathic sensitization.

TRPA1 regulates resting $[Ca^{2+}]_i$ levels in cortical astrocytes (Shigetomi et al., 2011) and was localized to Müller cells with immunohistochemistry (Araújo et al., 2020), but functional validation is lacking.

TRPM3 may be expressed in mouse Müller glia, with potential roles in gliotransmitter release (Webster et al., 2020).

TRPP1 was proposed to regulate osmotic swelling in Müller cells (Vogler et al., 2016).

TRPC4 antibodies labeled vimentin-positive radial processes in the chick retina (Crousillac et al., 2003), and *Trpc5* transcripts and immunosignals were detected in INL/GCL layers in the mouse retina (Oda et al., 2020; Witkovsky et al., 2008). There is no functional information about TRPC3-5,7 channels in Müller glia.

2.9. Summary

TRP channels in Müller cells, microglia and astrocytes regulate a vast range of context-specific signaling responses within which Ca^{2+} influx controls the transcriptome, metabolism, gliotransmitter and cytokine/chemokine release. The most studied isoforms, TRPC1 and TRPV4, have been linked to glial sensing of the biomechanical milieum regulation of blood-retina barrier and reactive gliosis. The function of the majority of TRP subunits expressed in retinal glia remains unknown.

2.10. TRP channels in the retinal pigment epithelium

Regulation of TRP channel activity is advantageous because it generates multimodal signal pathways by the same TRP channel. As the retinal pigment epithelium (RPE) serves many functions in maintaining photoreceptor function (Bok, 1985; Strauss, 2005), we hypothesize that the multimodal TRP channels are ideal for coordinating these different functions.

2.11. Ca^{2+} conducting ion channels in the RPE: TRP channels show a large variety

The RPE supports the photoreceptor function in several ways (Bok, 1985; Strauss, 2005; Wimmers et al., 2007). Among these functions are epithelial transport of Cl^- and water from the retina to the blood side, phagocytosis of shed photoreceptor outer segments during their renewal process and the secretion of angiogenic, neurotrophic, or immunogenic factors. Evidence from several groups showed the Ca^{2+}-dependence of these functions (Strauss, 2005; Wimmers et al., 2007). For that reason, RPE expresses a variety of Ca^{2+}-conducting ion channels, among them voltage-dependent Ca^{2+} channels and TRP channels. There are independent reports of the TRP channel expression pattern in the RPE, but these papers do not seem to support each other. Marked differences appear primarily at the mRNA and Western blot/immunohistochemistry levels. Zhao et al. used an RPE model based on human fetal cells (Zhao et al., 2015) to report the expression of TRPC4, TRPM1, TRPM3, TRPM7 and TRPV4 at the mRNA and Western blot levels. TRPM3 was found at the primary cilium, TRPV4 in the apical microvilli. TRPM3 and TRPC4 are localized close to the tight junctions. The group tried to show the functional role by measurements of transepithelial transport parameters such as transepithelial resistance and voltage. Although they showed that the broad range TRP blocker La^{3+} inhibited transepithelial transport by 70%, the group could not identify a specific contribution from a specific TRP channel isoform. Bollimuntha et al. added the expression of TRPC1 in ARPE19 cells (Bollimuntha et al., 2005). The expression of TRPM3 was supported by Gilliam and Wensel (2011) but not found in another study (Brown et al., 2015). The expression of TRPC4 and TRPV4 was supported by data from Crousillac and colleagues (Crousillac et al., 2003). Based on the use of antibodies, Gilliam et al. verified the expression of TRPM3 but could not confirm the expression of TRPV2 (Gilliam and Wensel, 2011). Kennedy et al. reported the expression of TRPV5 and 6 and tried to verify this in recordings of intracellular free Ca^{2+} (Kennedy et al., 2010). Using large (up to 5 mM) increases in extracellular Ca^{2+}, the group evoked responses of intracellular free Ca^{2+} sensitive to the nonselective TRP channel blocker ruthenium red. The group of Mitchell demonstrated functional expression of TRPML1 channels in mouse primary cell culture RPE cells, in ARPE-19 cells and in human embryonic stem cell based RPE cells (Beckel et al., 2018; Gómez et al., 2018). We studied TRP expression profiles in freshly isolated human primary culture RPE cells as well in RPE cells from mouse and pig in primary culture. Our published and unpublished data support the observations at the mRNA level (Barro-Soria et al., 2012; Cordeiro et al., 2010; Reichhart et al., 2015b; Wimmers and Strauss, 2007) (Fig. 4A). We found the expression of *Trpc1*, 4, 7; *Trpm1*, 2, 3, 7; *Trpv1-4* (but not V5, V6). The verification at the functional level exists so far for only a few TRP channels in the RPE.

2.12. Functional evidence of TRP channels in the RPE

The direct evidence for the activity of TRP channels in the RPE stems from patch-clamp experiments and measurements of intracellular free Ca^{2+} with Ca^{2+}-imaging techniques using Ca^{2+}-sensitive fluorescence dyes such as fura-2. These methods provided functional evidence for the activity of TRPC and TRPV2 channels.

TRPC1/4: When investigating the Ca^{2+} permeability of the plasma membrane for Ca^{2+} in the human RPE (human primary and ARPE19 cell cultures) under resting conditions, we

were surprised to find that TRPC channels are tonically active (Wimmers and Strauss, 2007). The mean value of the basic level of the intracellular free Ca^{2+} concentration in the RPE was measured at 100 nM. The Ca^{2+}-sensitive fluorescence dye used in these measurements is distributed throuough the complete inner space of the cell. It might be possible that there are subcellular spaces in the RPE with much higher intracellular Ca^{2+} concentrations; although this has not been investigated so far. Under these conditions, in the absence of active second-messenger pathways, inhibition of L-type channels had no effect on the Ca^{2+} level whereas La^{3+}, Gd^{3+} or Ni^{2+} reduced the baseline intracellular Ca^{2+} concentration down to 20 nM. A concentration/effect curve showed a half-maximal effect of La^{3+} at a concentration of 1 μM. In addition to TRP channels, ARPE19 cells functionally express voltage-dependent L-type channels of the Cav1.3 subtype as another type of Ca^{2+} conducting channel (Reichhart et al., 2015a). L-type channels might be inhibited by La^{3+}, Gd^{3+} or Ni^{2+} as well but a specific inhibition of these channels by dihydropyridines had no effect on the intracellular free Ca^{2+} baseline levels. Sensitivity to La^{3+}, Gd^{3+} and Ni^{2+} indicates TRP channel activity at baseline conditions. To obtain more insight into the TRP subtype, we tested the effects of blockers SKF96365 and 2-APB at concentrations of 50 μM and 75 μM, respectively. Similar to La^{3+}, SKF9365 and 2-APB reduced basal $[Ca^{2+}]_i$ to 20–50 nM. As TRPM channels are Ni^{2+}-insensitive (Penner and Fleig, 2007; Enyeart et al., 2002) and TRPV channels are activated by 2-APB (Hu et al., 2004; Clapham et al., 2005), the effects of blockers on baseline $[Ca^{2+}]_i$ can be attributed to TRPC channels. The subtype(s) of TRP channels that provide the Ca^{2+}-conductance under basal conditions remain to be ascertained.

TRPV2: Our PCR results indicated the expression of heat-sensitive TPRV channels in human RPE. To show the contribution of these channels to the Ca^{2+} signaling, we developed an experiment in which we could provide a rapid and short-time temperature increase of the extracellular milieu at different values while we measured intracellular free Ca^{2+} (Cordeiro et al., 2010; Reichhart et al., 2015b). We were able to evoke an increase in intracellular free Ca^{2+} with temperature pulses to 56 °C and in membrane conductance with temperature pulses to 45 °C (higher temperatures destabilize the whole-cell configuration), a temperature range specific for TRPV1 and TRPV2 channels. At temperatures of 56 °C, a larger contribution by TRPV2 in Ca^{2+} rises is expected. La^{3+} and ruthenium red blocked temperature-evoked Ca^{2+} transients whereas high concentrations of 2-APB evoked large $[Ca^{2+}]_i$ elevations.

Downregulation of TRPV2 expression by anti-TRPV2 siRNA reduced the temperature-evoked Ca^{2+} transients by the same magnitude as mRNA reduction. In whole-cell recordings of the patch-clamp technique, we showed that an increase in extracellular temperature induced a mildly rectifying current with a ruthenium red-sensitive inward component. Activation at high temperatures, block by La^{3+}/ruthenium red, Ca^{2+} rises in response to 2-APB and current/voltage relation of whole-cell currents substantiated the functional expression of TRPV2 channels in the RPE (Cordeiro et al., 2010; Hu et al., 2004). The TRPV1 agonist capsaicin and the TRPV3 agonist camphor (Clapham et al., 2005) had no effects on intracellular Ca^{2+}. Thus, TRPV2 appears to be the main thermoTRP channel in RPE cells.

2.13. RPE functions that are regulated by Ca^{2+} signaling: potential roles of TRP channels

Among the different functions of the RPE, the ones with evidenced Ca^{2+}-signaling as major regulator are epithelial transport of Cl^- and water, the circadian regulation of phagocytosis of shed photoreceptor out segments and secretion of growth factors (Wimmers et al., 2007). For epithelial transport and for regulation of secretion exist functional data that indicated a contribution of TRP channels. For phagocytosis the data for contribution of TRP channels are rather weak.

2.13.1. Transepithelial transport regulation by an unknown TRP channel—

Epithelial transport of water is driven by a transepithelial gradient of Cl^- across the RPE and serves to eliminate water from the outer retina. The transport starts with a net uptake of Cl^- by the $Na^+/2Cl^-/K^+$-co-transport across the apical membrane into the RPE cell to establish a high intracellular Cl^- concentration. Cl^- leaves the cell across the basolateral membrane through a variety of Cl channels towards the blood side driven by a transmembrane gradient for Cl^- and among these basolateral Cl channels are Ca^{2+}-activated Cl channels. Transepithelial Cl^- transport can be induced by increasing intracellular free Ca^{2+} with an apical application of ATP (Peterson et al., 1997). Indeed, Zhao et al. showed that transepithelial transport parameters in Ussing chamber experiments of a fetal RPE-based RPE model might depend on the activation of TRP channels by inhibitory effects of La^{3+}, a broad-range TRP channel blocker (Zhao et al., 2015), suggesting involvement of a TRP subtype. However, it is unclear whether the RPE cell model used in the study by Zhao represents the mature RPE.

2.13.2. TRPV2 channels in the RPE: a multitude of activation mechanisms and functions—

The contribution of TRPV2 channels to the regulation of RPE function gives a good example of how TRP channels have different activation pathways and that each activation pathway results in different RPE cell reactions (Fig. 4). In general, two different mechanisms activate TRPV2 channels in heterologeous expression and in the RPE (Kanzaki et al., 1999; Reichhart et al., 2015b). One of the direct activation mechanism acts by increasing the current through the ion channel pore; the other acts through an increase in the surface expression of the channel proteins. When elucidating the activation mechanisms for TRPV2 in more detail, we used a heat pulse to 45 °C to increase whole-cell currents as well as $[Ca^{2+}]_i$ (Fig. 4 B) in RPE cells and used the increased membrane conductance as a specific measure of functionally available TRPV2 channels in the plasma membrane. However, given that such temperature shifts do not commonly occur in the retina, we investigated TRPV2 activating pathways (Fig. 4 C). When stimulating the cells with IGF-1, we found that heat and IGF-1 activated TRPV2 in the same order of magnitude. In contrast, cannabidiol did not change the membrane conductance while it increases the response to heat-evoked stimulation. The total activatable TRPV2 membrane conductance is larger with cannabidiol than without. Thus, the effects of cannabidiol seem to be limited to increasing TRPV2 channel density in the plasma membrane. Using an immunocytochemistry-based assay, we analyzed the surface expression of TRPV2. Cannabidiol increased the surface expression by 4-fold whereas IGF-1 by ~2-fold. Thus, IGF-1 increases the membrane conductance by both TRPV2 channel activity and surface expression whereas cannabidiol

increases surface expression only. However, given that such temperature shift do not commonly occur in the retina, we investigated TRPV2 activating pathways.

Together with heat, we identified three agonists that activated TRPV2 channels as part of Ca^{2+}-signaling cascade. In whole-cell recordings of the patch-clamp technique and measurements of intracellular free Ca^{2+}, we demonstrated that insulin-like growth factor-1 (IGF-1) strongly activates TRPV2 in human RPE cells. In mouse RPE cells, we showed that TRPV2 contributes to angiotensin-2 evoked Ca^{2+} signals under the contribution of angiotensin- receptor associated protein (ATRAP) (Barro-Soria et al., 2012) (Fig. 4D). TRPV2 channels may also contribute to immune-related Ca^{2+} signaling. Using human serum as a source for activated complement proteins, we found that RPE cells react with a highly reproducible Ca^{2+} signal that integrates the activities of the different complement proteins including anaphylatoxins and terminal complex (Genewsky et al., 2015). This signal was blocked by ruthenium red and by isradipine and nifedipine further implicating TRPV2 channels and voltage-dependent L-type channels. Furthermore, an investigation of anaphylatoxins-activated Ca^{2+} transients in RPE cells revealed that TRPV2 channels mainly contribute to the signal pathways of C3a and C5a receptor activation because anaphylatoxins-evoked Ca^{2+} rises were insensitive to nifedipine, an L-type channel blocker (Busch et al., 2017). IGF-1 and the anaphylatoxins-dependent activation of TRPV2 channels are both mediated by the activation of PI3-kinase.

The multimodal activation of TRPV2 enables the participation into a variety of functional changes in the RPE. Stimulation of RPE cells with angiotensin-2 results in a reduction of renin expression and secretion by RPE cells via activation of AT1 receptor and an increase in intracellular free Ca^{2+} (Barro-Soria et al., 2012). Using a siRNA approach to reduce the TRPV2 channel expression in primary cultures of porcine RPE cells, we showed reduced angiotensin-2-evoked Ca^{2+} transients (Barro-Soria et al., 2012). Thus, the angiotensin-2-dependent Ca^{2+}signals require TRPV2 activation. In animal studies, we showed that the renin production by the RPE controls the local renin-angiotensin-system in the retina (Milenkovic et al., 2010). Thus, the TRPV2 channel in the RPE is essential to regulate intraretinal renin-angiotensin system.

Complement-evoked Ca^{2+} signals in the RPE also lead to changes in secretion (Genewsky et al., 2015; Busch et al., 2017). The complement component C5a activates intracellular Ca^{2+} signals that are dependent on PI3-kinase activation sharing the same siganling pathway than IGF-1 (Busch et al., 2017). This leads to increased C3 expression in RPE cells as well and secretion of MCP1, VEGF-A and IL-8 (Busch et al., 2017). VEGF-A secretion is also under TRPV2-dependent control by IGF-1 (Cordeiro et al., 2010). Either increase in temperature or IGF-1 lead to an increased release of VEGF-A by the RPE. The observation that heat increases the VEGF- A secretion might have an implication for our understanding of the effects of laser treatment of the retina. Areas that are not directly affected by the laser but receive a heat impact might change the secretion by RPE cells through activation of TRPV2 channels.

2.13.3. Unknown functions of TRP channels for RPE physiology—The basal intracellular Ca^{2+} concentration is at a “physiological” concentration level of 100 nM,

presumably due to tonic activity of TRPC1/4 channels (Wimmers and Strauss, 2007). Constant Ca^{2+} influx must be counterbalanced by ATP-driven Ca^{2+} clearance and/or sequestration. Indeed, we found that inhibition of PMCAs (plasma membrane Ca^{2+}-ATPases) strongly elevates $[Ca^{2+}]_i$. We speculate that tonic Ca^{2+} influx quickly delivers Ca^{2+} to the extracellular space, most likely to the retinal side, as TRPC4 channels were located on the apical membrane of RPE cells. Ca^{2+} release across the apical membrane might thus serve for Ca^{2+}-dependent signaling mechanisms in the photoreceptor outer segments.

Cultured RPE cells from mouse or human functionally express TRPML1 channels (Beckel et al., 2018; Gómez et al., 2018). These channels seem to participate in intracellular Ca^{2+} signaling involing lysosomes integrated in to toll-receptor signaling. The group discussed the potential functional relevance for RPE cells but further evidence is lacking.

2.14. Summary

Own data and data from other groups suggest a large variety of TRP channels expressed in the RPE. Most of the data are at the mRNA level, evidence of protein expression or functional validation are still lacking. So far, the best investigated channel is the TRPV2 in terms of regulation, functional role and functional analysis. Functional evidence exists for TRPC channels. For the majority of TRP in the RPE exists a large gap of knowledge.

3. TRP expression in microglia

As the resident immune cells of the brain and retinal parenchyma, microglia continually monitor tissue homeostasis and respond to a wide variety of stressors by transitioning into a reactive state to orchestrate the inflammatory response (Prinz et al., 2019). Under healthy circumstances, microglial phagocytosis of dying cells, debris and pathogens and secretion of cytokines/chemokines help limit the spread of tissue damage, modulate neurogenesis and prune excess synapses, whereas overactivation promotes retinal injury (Li and Barres, 2018; Silverman and Wong, 2018). Mild local insults attract microglial processes and affect synaptic remodeling without unleashing a full-blown reactivity, whereas strong activation occurs within a neurodegeneration-promoting context associated with cytokine release (Silverman and Wong, 2018). Calcium is essential for microglial chemotaxis, with changes in $[Ca^{2+}]_i$ correlating with process motility in intact retinas (Redmon et al., 2021). We propose that TRP channels work together with P2X and Orai channels as the main modes of plasmalemmal Ca^{2+} influx in retinal microglia.

3.1. The transcriptional profile for TRP genes in retinal microglia diverges from CNS expression

A comparison of vanilloid subfamily expression in retinal vs. cortical microglia shows a remarkable divergence. Retinal cells show the following expression sequence: *Trpv2> Trpv1> Trpv3> Trpv4* whereas their cortical cognates exhibit *Trpv4> Trpv6> Trpv2>> Trpv3> Trpv1* (Redmon et al., 2021). Overall *Trpv* abundance in the retina is markedly lower *vis a vis* cortex (Fig. 5A), an observation consistent with the reported variability between microglial sensomes across the CNS (Bennett et al., 2018;

De Biase and Bonci, 2019). Thus, retinal microglia likely sense and respond differently to biomechanical and chemical cues than their cortical and PNS counterparts.

3.2. TRPV4 mediates the microglial response to osmotic and mechanical inputs

Low TRPV4 expression in retinal microglia relative to RGC and Müller glial expression (Figs. 5 and 9B) caused it to be missed in early immunohistochemical analyses (Ryskamp et al., 2011). The expression was subsequently unmasked with lineage-specific markers and 2-photon microscopy (Redmon et al., 2021) which demonstrated it for both reactive and quiescent microglia (Fig. 5B). TRPV4-mediated calcium influx correlated with retraction of secondary and tertiary processes but without significant changes in surveillance. Interestingly, TRPV4 agonists suppressed lamellipodial ruffling in primary microglial cultures (Redmon et al., 2021). Mechanisms that mediate microglial surveillance may be distinct from those that serve motility.

The high input resistance, low resting conductance and low $[Ca^{2+}]_i$ in unstimulated retinal microglia (Redmon et al., 2021) predict that the cells' membrane potential and $[Ca^{2+}]_i$ will be impacted by even a limited amount of cation Ca^{2+} influx. Small (10–20 pA) TRPV4 currents were indeed associated with substantial $[Ca^{2+}]_i$ increases and significant (~10 mV) hyperpolarizations presumably mediated by a Ca^{2+}-activated potassium conductance. Perfusion of intact retinas with the TRPV4 antagonist HC06047 at room temperature did not affect microglial $[Ca^{2+}]_i$, resting membrane potential or branching but microglial motility might be TRPV4-dependent at body temperature (Nishimoto et al., 2021). Similar to Müller cells, microglial TRPV4 activation requires eicosanoid signaling (Redmon et al., 2021).

3.3. TRPV1 may be involved in inflammatory activation

Cortical microglia express TRPV1 channels, which may contribute to proinflammatory cytokine release, oxidative stress, and neurotoxicity (Marrone et al., 2017). TRPV1 has been similarly linked to pressure-induced release of the proinflammatory cytokine IL-6 from retinal microglia (Sappington and Calkins, 2008). Functional analyses of calcium signaling in these cells show substantial $[Ca^{2+}]$i responses to the TRPV1 agonist capsaicin (Fig. 5C). The channel may be functionally active in plasma membrane as well as intracellular compartments (Miyake et al., 2015).

3.4. Summary

Low *Trpv* expression in retinal microglia may reflect the specifics of the retinal biomechanical milieu in which cells must contend with IOP fluctuations and ionic changes associated with the tonic activity of ON and OFF pathways. TRPV channels equip microglia with responsiveness to mechanical and chemical stimuli, with potential roles in retinal inflammatory signaling.

4. The *Drosophila* Trp channels: signal transduction cascade in the photoreceptor

4.1. An introduction

The "A-type" *Drosophila* mutation, isolated by Cosens and Manning shows a transient light response in the fly's electroretinogram (Cosens and Manning, 1969). Thus, the signaling cascade that transduces light into an electrophysiological signal is active but is not maintained active in the mutant fly. Baruch Minke and colleagues demonstrated that the phenotype is based on a transient photoreceptor potential (Trp) based on a defect in signal cascade and gave the mutation the name Trp (Barash et al., 1988; Minke, 1977, 1982, 2002; Minke et al., 1975; Selinger and Minke, 1988). The defective gene was isolated and, at the end of 1989, identified as an integral membrane protein with unknown function (Montell and Rubin, 1989; Wong et al., 1989). Its identification as ion channel that conducts Na^+ and Ca^{2+} was achieved 3 years later by Hardie and Minke (1992). This gene turned out to be a founder of a complete gene family of homologs in the vertebrate system (Wes et al., 1995; Zhu et al., 1995). The product of the TRP gene codes for an ion channel that conducts Ca^{2+} and Na^+, generating the light-induced current (LIC) in the *Drosophila* photoreceptor. Upon opening of this channel, the membrane potential of the photoreceptor becomes depolarized. The TRP channel would permit a constant depolarization during the period of illumination. This property fails due to the mutation (Hardie and Minke, 1992).

The research on *Drosophila* TRP activation/deactivation showed that the unique property of all TRP channels, the multimodal regulation, is fully exploited to generate and fine-tune the LIC (Hardie and Juusola, 2015; Hardie and Raghu, 2001; Katz and Minke, 2018; Montell et al., 2002). The research relies on detecting and functional analysis of more genes that change photoreceptor activity when mutated (Pak and Leung, 2003). Furthermore, proteins were analyzed in heterologous expression systems. Of great advantage was the unique structural arrangement of the light transduction cascade-forming proteins (Voolstra and Huber, 2020). This arrangement permitted the analysis of the complete light transduction cascade in one membrane patch from the photoreceptors' light-sensitive compartment, the rhabdomere (Minke and Parnas, 2006). This seems to be important as the analysis of *Drosophila* TRP channels in expression might result in confounding data (Lev et al., 2012). Still, basic questions need clarification. However, the specialized activation and gating regulation modalities of *Drosophila* TRP channels substantially contribute to the fly photoreceptor's unique properties (Voolstra and Huber, 2020; Hardie and Raghu, 2001; Katz and Minke, 2018).

4.2. The light-evoked signaling transduction cascade in Drosophila; an overview

The structure of the *Drosophila* photoreceptor resembles that of vertebrates (Hardie and Raghu, 2001). Attached to a cell body is a compartment with a greatly enlarged surface area that contains densely packed proteins of the light transduction cascade. Its evolutionary origin is distinct from photosensitive compartments in vertebrates. The vertebrate photoreceptor outer segment evolved from a cilium, whereas the *Drosophila* rhabdomere evolved from microvilli. Vertebrate photoreceptors hyperpolarize upon light perception whereas *Drosophila* photoreceptors depolarize. The *Drosophila's* photoreceptor

light response results from a lipid-based signal transduction cascade ignited by light-dependent activation of *Drosophila* rhodopsin that, in turn, activates phospholipase Cβ4 (PLCβ4) through a Gαq G-protein subunit. PLC generates inositol-1,4,5-trisphosphate (InsP3) and diacyl glycerol (DAG) from phosphatidylinositol-4,5-bisphosphate (PIP_2), a membrane lipid (Cook et al., 2000; Devary et al., 1987; Hardie et al., 2015; Hardie and Juusola, 2015; Katz and Minke, 2018; Katz et al., 2017; Minke, 2012; Minke and Selinger, 1992; Montell et al., 2002; Raghu et al., 2012; Tian et al., 2012; Voolstra and Huber, 2020). These metabolites amplify the single-photon response and serve critical roles in photoreceptor depolarization. DAG activates protein kinase C (eye-specific PKC) and represents a substrate to refill PIP_2 levels in the plasma membrane (Balakrishnan et al., 2015; Voolstra et al., 2017). PKC itself signals inactivation and adaptation. The reduced concentration of PIP2 in the plasma membrane, which changes its lipid packing, generates mechanosensitive force by a *force-from-lipid mechanism* (Cox et al., 2019) that may activate TRP in the rhabdomere membrane (Hardie and Franze, 2012). TRP activity itself is additionally facilitated by rise in intracellular Ca^{2+} but gets inactivated at higher Ca^{2+} concentrations (Hardie, 1991; Chu et al., 2013a; Hardie and Juusola, 2015; Hardie and Raghu, 2001; Katz and Minke, 2012). InsP3 might have several roles in light transduction cascades of insect photoreceptors. InsP3 activates a release of Ca^{2+} from intracellular Ca^{2+} stores upon binding to the InsP3 receptor, a ligand-gated intracellular Ca^{2+} channel. In bees or the ventral photoreceptors of *Limulus,* intracellular Ca^{2+}-rises resulting from InsP3 receptor activation represent a significant proportion of the overall light-induced Ca^{2+} signal that amplifies TRP activity (Brown and Blinks, 1974; Walz and Baumann, 1995; Walz et al., 1995). In *Drosophila*, InsP3 receptor-dependent Ca^{2+} release seems not to be a part of the light transduction cascade (Acharya et al., 1997). It might contribute to adjustment of the photoreceptor's light sensitivity, a hypothesis that is not fully proven as publications about the problem are still controversial (Voolstra and Huber, 2020). However, the understanding of the role of essential signaling molecules and their metabolites is originated/verified by analysis of different *Drosophila* mutations: ninaE ("neither inactivation nor afterpotential E") for rhodopsin, norpA ("no receptor potential A") for PLCβ4, inaC ("inactivation no afterpotential C") for PKC, rdgA ("retinal degeneration A") for DAG kinase (Pak and Leung, 2003).

The mutation inaD ("inactivation no afterpotential D") is not among the genes that directly contribute to the light transduction cascade (Montell and Montell, 1998; Montell, 2012; Pak et al., 2012; Tsunoda and Zuker, 1999; Wang and Montell, 2007). However, it plays a vital role for the unique properties of the *Drosophila's* light transduction cascade. The photoreceptor response to light shows fast kinetics, with high specificity, sensitivity, and reproducibility (Chu et al., 2013a; Henderson et al., 2000). The single photon-response of the *Drosophila* photoreceptor is five times larger than in mammalian rods. Its kinetics - a fully processed reaction within 0.1s - is five times faster than that of mammalian rods (Hardie and Raghu, 2001). These qualities are associated with function of inaD, a scaffolding protein (Sanxaridis et al., 2007; Wang et al., 2005a) that assembles via five PDZ domains (PDZ = post-synaptic density protein). PSD-95, disc large tumor suppressor 1 (dlg1) and zona-occludens1 (ZO-1) may assemble into a "transducisome" or "signalplex" (Wang and Montell, 2007) that includes the G-protein Gαq subunit, PLCβ4, PKC and TRP.

In this way, inaD ensures the high concentration of the light transduction proteins, their stoichiometry and diffusion-less interaction with, therefore, high-speed light transduction. Recent studies showed that this complex is not a fixed entity and might underlie regulatory changes that possibly modulate the light transduction cascade. Several studies led to the hypothesis that the activation of the light transduction cascade also leads to a conformational change of inaD. However, functional role of this mechanism remains unclear. Patch-clamp analysis of the light-evoked photoreceptor response has proven this signaling complex's functional relevance (Delgado et al., 2019; Minke and Parnas, 2006). Here, excised patches from the rhabdomere membrane can fully generate a light response. This type of investigation has led essential advances in the understanding of the regulation of TRP channels during the light response.

4.3. TRP and TRPL in phototransduction

4.3.1. Ion permeability of TRP channels in Drosophila photoreceptors—The LIC is generated by two TRP channels, TRP and TRPL (Niemeyer et al., 1996; Reuss et al., 1997). To date, the literature describes three TRP channel proteins in the *Drosophila* photoreceptors (Hardie, 2014; Hardie and Juusola, 2015; Katz and Minke, 2018; Minke and Parnas, 2006; Raghu and Hardie, 2009), with the TRP family related to the vertebrate TRPC group (Raghu and Hardie, 2009). The TRPC channels in vertebrates are the ones with the highest homology to the *Drosophila* TRP's (Clapham et al., 2005). TRP activation generates light-dependent photoreceptor depolarization at a more significant proportion than TRPL. The third Trp gene, Trpγ, has no known function. The investigation of the functional properties of these channels is not easy as they change their properties depending on the expression system (Lev et al., 2012; Minke and Parnas, 2006). The TRP channel subunits generally form tetramers to build a functional channel. Indeed, Montell's group concluded from co-immunoprecipitation experiments with heterologously expressed TRP- and TRPL-proteins and from *in situ* analysis of Drosophila photoreceptors that TRP and TRPL form heterotetramers. This conclusion was challenged by *in vivo*/*in situ* data. Co-immunoprecipitation experiments and the binding affinities to the scaffold protein inaD concluded that only TRP binds to inaD and that therefore TRP and TRPL subunits form only homotetramers and not heterotetramers as known for other members of the mammalian TRPC family (Bahner et al., 2002; Chevesich et al., 1997; Paulsen et al., 2000; Tsunoda et al., 1997). This is supported by the observation that only TRPL shows a light-dependent regulation of surface expression that would not function when TRP and TRPL form heterotetramers (Bahner et al., 2002; Niemeyer et al., 1996). However, Bahner et al. and Xu et al. (Bahner et al., 2002; Xu et al., 1997) considered the existence of both homotetramers and heterotetramers of TRP and TRPL. Given the observation that TRP is expressed in large excess over TRPL, the TRP/TRPL heterotetramers represent a smaller proportion among the functional channels and their possible existence was challenged by Katz et al. (2013). The role of TRPγ is unknown, but it might possibly form heterotetramers with TRPL (Xu et al., 2000; but see Katz et al., 2017). TRP and TRPL strongly differ in their permeability properties.TRP shows a 50-fold higher permeability for Ca^{2+} than for Cs^{+} whereas for TRPL, this permeability ratio is 4:1 (Chu et al., 2013b; Liu et al., 2007; Reuss et al., 1997). The trp mutation leads primarily to a loss of Ca^{2+} permeability (Hardie and Minke, 1992). These data stem only from *in vivo* measurements because TRP needs inaD

to form tetramers to build a full functional channel pore and cannot be investigated as an isolated channel in heterologous expression systems. Furthermore, *in vivo* TRP current recordings are impossible in the absence of Na^+ because this leads to a fast Ca^{2+} overload and disruption of the cell so that the permeability ratio of Ca^{2+} versus monovalent cations is estimated in a bi-ionic approach. Thus, the permeability ratio is given as Ca^{2+}/Cs^+. The TRP/TRPL channel activation might occur by mechanical forces in the plasma membrane and by phosphorylation, as there are 28 possible phosphorylation sites in the TRP protein (Voolstra et al., 2013). Phosphorylation of TRP is light-dependent and seems important for shaping LIC under flicker light conditions (Voolstra et al., 2010, 2017). As described below, TRP/TRPPL activation by light may be associated with mechanical forces inside the plasma membrane, and protons.

4.3.2. Effects of Na^+ and Ca^{2+} entering the photoreceptor cell—Photoreceptor stimulation by light generates LIC representing the combined activity of TRP, TRPL (Leung et al., 2000; Niemeyer et al., 1996), and the Na^+/Ca^{2+} exchanger (Wang et al., 2005b). The proportion of Ca^{2+} in the LIC was estimated between 26%, and thus Na^+ influx mediates the majority of transmembrane flux across the rhabdomere membrane (Chu et al., 2013b). On one hand, permeability ratio for Ca^{2+}/Na^+ of the TRP and of TRPL accounts for proportion between Ca^{2+} and Na^+flux in the LIC. The Ca^{2+} permeability of TRP is about 50 times higher than that for monovalent cations. (Reuss et al., 1997). However, the permeability of TRPL for Ca^{2+} is only about 4 times higher that for Na^+ (Liu et al., 2007). In this way, TRPL contributes significantly to LIC. The ratio of Na^+/Ca^{2+} in the extracellular fluid of the rhabdomere is 120/1.5 mM (Hofstee and Stavenga, 1996) and increases the proportion of Na^+ in LIC. Thus, Ca^{2+} stimulates LIC and the Na^+ flux in LIC generates the receptor potential that represents the physiological equivalent of light. The receptor stimulates the release of histamine from the photoreceptor synapse (Gengs et al., 2002) to spread the signal into the visual information computing neuronal network.

The increase in $[Ca^{2+}]_i$ that results from the proportion of Ca^{2+} in the LIC serves many functions determined by the different Ca^{2+}-dependent proteins. We refer the reader to excellent reviews by Hardie and Raghu, Voolstra and Huber or Minke or Montell for more detail (Gutorov et al., 2019; Hardie and Juusola, 2015; Katz and Minke, 2018; Montell et al., 2002; Voolstra and Huber, 2020). Ca^{2+} modulates the rhodopsin cycle and the chain of interacting proteins in the light transduction cascade. Positive and negative Ca^{2+} -mediated feedback mechanisms regulate acceleration of the light response, light sensitivity, light adaptation, and termination of the photoreceptor response. Ca^{2+} also triggers a light-dependent “pupil mechanism” by activating myosin V-dependent migration of pigment granules from the cytosol towards the rhabdomere basement (Satoh et al., 2008). At concentrations lower than 1 μM, Ca^{2+} accelerates the light transduction cascade by activating PLC, TRP and PKC whereas higher concentrations of Ca^{2+} inhibit the phototransduction cascade. The rhodopsin cycle includes activation and deactivation of rhodopsin as well as the exchange of retinal isomers. Thus, regulation of TRP activity and its ability to increase intracellular free Ca^{2+} is of central importance for photoreceptor function.

4.3.3. Regulation of TRP/TRPL activity and its role in photoreceptor function

—The plasma membrane of the rhabdomere contains two types of TRP channels, TRP and TRPL. Both have different ion permeability properties and serve different roles in photoreceptor signal transduction. Loss-of-function mutation of TRP has a greater impact onto the photoreceptor potential than TRPL (Gutorov et al., 2019; Hardie and Juusola, 2015; Katz and Minke, 2018; Minke, 2002; Raghu and Hardie, 2009). Different experimental approaches have led to different conclusions and interpretations of the data and the precise sequence of molecular steps remains to be ascertained.

The activity of TRP and TRPL channels in the dark: Isolated photoreceptors that are prepared and separated from the pigmented cells show spontaneous activity in the dark that requires TRP and TRPL channels (Hardie and Minke, 1994). Hardie and Minke followed the hypothesis that this effect might be due to an inefficient inhibition of TRP and TRPL under metabolic stress. They showed that anoxia or uncoupling of mitochondrial ATP production leads to TRP/TRPL activation in recording from photoreceptor preparations (Agam et al., 2000; Minke and Agam 2003), a conclusion that was supported by Hardie et al. (2003). PKC seems to be one of the critical enzymes for this effect (Agam et al., 2004). A reduction in intracellular ATP leads to reduced PKC activity and subsequent spontaneous active TRP/TRPL in the dark. Further evidence for the role of PKC comes from experiments in which intracellular Ca^{2+} buffering by BAPTA completely abolished the effects of ATP depletion (Agam et al., 2004). Another pathway for metabolism-induced spontaneous TRP/TRPL activity links PLC activity and TRP/TRPL activation (Hardie et al., 2003). Here, Hardie and colleagues suggest a model in which ATP depletion reduces the turnover of DAG to regenerate PIP_2 by DAG kinase. Increased levels of DAG lead to a higher number of active TRP/TRPL. Studies of spontaneous photoreceptor activity in the dark are thus important for the understanding of TRP/TRPL activation in response to light.

The light-dependent activation of TRP: The light-dependent activation mechanisms for TRP/TRPL determine LIC's properties, amplitude and kinetics. Several parallel acting pathways serve different functions to activate TRP/TRPL. The initial and basal activation occurs via the lipid metabolism. Initiation of lipid metabolism occurs via light-dependent activation of PLC that cleaves DAG and InsP3 from PIP_2 (Hardie, 2003, 2004). DAG itself possibly mediates the excitation of the photoreceptor by activation of TRP/TRPL channels. Evidence of DAG's role in activating TRP came from a mutation that leads to photoreceptor degeneration in *Drosophila*. The rdgA gene mutation leads to blindness in *Drosophila*. Interestingly, a rdgA/trp or a rdgA/norpA (norpA = PLC) double mutant rescue photoreceptors from degeneration (Raghu et al., 2000). Ca^{2+} that enters the photoreceptor cell can explain the effect (Bloomquist et al., 1988; Hardie et al., 2003). The rdgA codes for DAG kinase that is inactive due to the mutation. This leads to DAG accumulation and subsequent overstimulated TRP channels. In turn, the overstimulated TRP channels lead to toxic overload of photoreceptor cells with Ca^{2+} with subsequent cell death. Non-functional TRP channels of the Trp mutant rescue the degenerative phenotype in the rdgA/trp double mutant because mutant TRP has lost its Ca^{2+} permeability (Hardie and Minke, 1992). In same way, the absence of PLC (norpA) prevents DAG accumulation so that DAG kinase activity has no effects on TRP activation (Hardie et al., 2003). How DAG leads to activation

of TRP/TRPL is not clear. Application of DAG to freshly isolated rhabdomers evoked a very small response that is in speed and amplitude not comparable to LIC (Delgado et al., 2014; Raghu and Hardie, 2009). Thus, DAG might not directly activate TRP by binding to the protein as is known from mammalian TRP channels. The second activation mechanism might result from its cleavage by DAG lipase. The products of this reaction, poly-unsaturated fatty acids (PUFA), might represent a parallel stimulator for TRP channels (Chyb et al., 1999; Parnas et al., 2009b). However, blocking DAG lipase is not blocking TRP channel activation (Delgado et al., 2014, 2019). Hardie et al. investigated TRP/TRPL activation *in situ* in photoreceptors from flies carrying a null mutant of PLC (norpA) (Hardie et al., 2003). In this study, TRP channels could be activated by the application of polyunsaturated fatty acids. However, the reaction is much weaker than the light-dependent stimulation of TRP. Thus, PUFA does not necessarily activate TRP channels in a direct manner. Work that is more recent further challenged the role of PUFA. Although Leung et al. showed that the NinaE gene functions as a DAG lipase localizing to the inner segment of the rhabdomere and that reduced levels in the mutant fly leads to abnormal light responses (Leung et al., 2008), the TRP/TRPL can still be activated and the PUFA levels do not change after light stimulation (Delgado et al., 2014). A more recent publication showed that here might be the activating mechanism of polyunsaturated fatty acids. Randall et al. showed that changing the fatty acid composition in the *Drosophila* photoreceptors with a yeast diet that did not affect PLC activity leads to reduced light sensitivity and slower light-induced contractions (Randall et al., 2015). It might be possible that PUFAs have multiple targets in the photoreceptor cell that overcome the absence of PLC. The experiment with the double mutant rdgA/norpA suggests that PLC activation is essential for TRP activation (Hardie et al., 2003). If DAG can so far not be verified, the PLC-dependent PIP_2 depletion represents a major mechanism (Hardie et al., 2004). First, the PLC reaction produces protons that can lead to a significant acidification due to the narrow spaces in the rhabdomere microvilli (Huang et al., 2010). Acidification is a TRP activator. Second, the PIP_2 depletion generates mechanical forces in the plasma membrane because after PIP_2 degradation the plasma membrane requires less space and proteins move closer to each other. Indeed, atomic-force microscopy reveals light-induced shrinkage of rhabdomere microvilli (Hardie and Franze, 2012). That activates Trp channels but also other ion channels that are involved in the light transduction cascade, such as inward rectifier K^+ channels (Hardie and Franze, 2012). Also passively induced mechanical impacts onto the plasma membrane by hypotonic challenge activated TRPL (Parnas et al., 2009a). A recent review by Gutorov et al., (2019) concluded a role of the cholesterol content in the plasma membrane for termination of TRPL channel activity. The mechanism was detected by the effects of the drug methyl--β-cyclodextrin. TRPL channels are fast deactivated by methyl-β-cyclodextrin (Peters et al., 2017). Methyl-β-cyclodextrin leads to extrusion of cholesterol from the plasma membrane and therefore, to disruption of lipid rafts. This further supports the idea of TRP/TRPL activation by changes in the lipid environment of the plasma membrane. Protons and PLC-dependent PIP2 depletion are currently viewed the most important activators of TRP/TRPL (Gutorov et al., 2019; Huang et al., 2010) (Fig. 6).

The lipid-based activation mechanisms open in the single-photon response only a few TRP channels that might not be strong enough for a good signal-to-noise ratio to define

physiologically relevant photoreceptor response to one photon (Hardie and Juusola, 2015; Hardie and Raghu, 2001; Katz and Minke, 2018). An amplification step is required. (Hardie et al., 2002). The key for this amplification is the Ca^{2+} that enters the rhabdomere through the TRP channels. At concentrations up to 1 μM Ca^{2+} is an activator of TRP. In the initial phase of the light-response Ca^{2+} entering the rhabdomere opens more TRP channels that, in turn lead to more robust Ca^{2+} rise and depolarization of the photoreceptor. The exact mechanism how Ca^{2+} activates TRP/TRPL is not clear. As Ca^{2+} increases activate a variety of kinases it was hypothesized that Ca^{2+}/CaMK increases TRP/TRPL activity by phosphorylation. A recent paper concluded that CamK does not directly activate TRP/TRPL although these channel proteins harbor two CamK binding sites (Chen et al., 2021). A direct Ca^{2+} effect leading to TRP/TRPL activation is the most likely one. At this stage, Ca^{2+}-dependent dark noise reduction establishing an activation threshold for TRP/TRPL has to be overcome (Chu et al., 2013a; Katz and Minke, 2012). Calculations resulted in estimating 15 TRP channels being activated in the rising phase (first 10–20 ms; quantum bump) of single-photon response (Henderson et al., 2000). Furthermore, PLC shows a comparable Ca^{2+} dependence to TRP. With increasing intracellular Ca^{2+} concentrations, the light-evoked PLC activity increases up to 1 μM and decreases at concentrations higher than 1 μM (Running Deer et al., 1995). Thus, Ca^{2+} not only increases TRP open probability but also fosters PIP_2 depletion of the plasma membrane (Voolstra and Huber, 2020). Using computer-based modeling of TRP/TRPL activation, the role of Ca^{2+} and DAG kinase in the shape of LIC could be simulated (Pumir et al., 2008; Song et al., 2012).

Deactivation of TRP channels and termination of LIC: The generation of a physiologically relevant signal in response to one photon requires the precise activation of TRP/TRPL channels and the precise termination of the process and the deactivation process depends on the free intracellular Ca^{2+}. Due to the narrow space in the microvillus, even a relatively weak Ca^{2+} inward current will generate huge Ca^{2+} concentrations that go up to 200 μM (Oberwinkler and Stavenga, 2000). This high level terminates LIC and puts the photoreceptor into a refractive phase that will last for appr. 100 ms (Oberwinkler and Stavenga, 2000); until Ca^{2+} levels are decreased by Ca^{2+} extruding mechanisms such as the Na^+/Ca^{2+} exchanger (Voolstra and Huber, 2020). At high Ca^{2+} concentration, Ca^{2+}-dependent proteins maintain LIC in a refractive period. First, Ca^{2+}-dependent kinases, CamKII and PKC (due to ninaD being in close proximity of TRP and additionally activated by DAG) become activated at higher Ca^{2+} concentrations leading to TRP/TRPL inactivation upon channel phosphorylation (Hardie et al., 1993). Through the proximity of PKC and TRP, TRP becomes phosphorylated leading to Ca^{2+}-dependent inactivation (Hardie et al., 1993). Another important kinase is PLC (Balakrishnan et al., 2015; Gu et al., 2005; Hardie et al., 2004; Katz and Minke, 2012, 2018), with comparable Ca^{2+} sensitivity to TRP channel modulation (Running Deer et al., 1995). At concentrations below 1 μM PLC is activated by Ca^{2+}, whereas at higher concentrations (50 μM), it becomes inhibited. This would increase the PIP_2 abundance in the plasma membrane with subsequent TRP/TRPL deactivation. The increase in PIP_2 abundance is further supported by DAG kinase (rdgA). The first step to recycle DAG for PIP_2 regeneration is the phosphorylation of DAG by DAG kinase so that DAG-P can re-enter the PIP_2 synthesis (Balakrishnan et al., 2015; Hardie et al., 2015). Again, the increase of PIP_2 in the plasma membrane will reduce TRP/TRPL activity. In

the case of inactive DAG kinase (rdgA mutation), refilling of the PIP_2 levels is impaired and TRP activity cannot be reduced, leading to photoreceptor degeneration (Sengupta et al., 2013). The Ca^{2+}-dependence of PLC might explain the effect of the TRP mutation (Hardie et al., 2001). The absence of a Ca^{2+} influx through TRP and the low Ca^{2+} permeability of TRPL lead to a weak PLC activation and after a low PIP2 depletion of the plasma membrane so that the receptor potential cannot be maintained.

4.4. Regulation of TRP/TRPL channel activation by translocation from the plasma membrane

The above-described short-term regulation of the TRP/TRPL channel activity has limitations in adaptation of the photoreceptor activity to various constant light scenarios. Long-term regulation of TRP/TRPL activity for tuning photoreceptor sensitivity to work under constant light or darkness conditions might occur via modulation of the integration into the inaD complex and by translocation mechanisms that regulate the number of channels in the plasma membrane. Regulation by inaD modulation applies for the TRP channel. As a base, the integration into inaD is a prerequisite for TRP activity (Minke and Parnas, 2006), anchors the TRP channel in the plasma membrane as well as in the signaling complex with all advantages for fast and efficient light transduction (Tsunoda et al., 2001). However, it appears that the inaD complex is a rather dynamic complex that seems to be regulated by light too. Liu et al. (2011) demonstrated that the redox status of inaD changes upon illumination and affects the binding properties of the PDZ domains. The light-induced oxidation of the PDZ domain that binds to TRP results in the release of TRP from the inaD complex. However, although the integration of TRP into inaD is required for its activation, a significant physiological effect for this mechanism is unknown. TRPL is the channel that is regulated by its surface expression (Bahner et al., 2002). In the first few minutes under constant light TRPL is moved away from the “signalplex” to the basement of the rhabdomere and from there TRPL is transported over the next hours in vesicles to the basolateral membrane (Cronin et al., 2006; Oberegelsbacher et al., 2011). TRPL is not subjected to digestion/degradation because the total of TRPL stays constant (Bahner et al., 2002). Rearing in the dark for 2 h redistributes TRPL into the plasma membrane of the rhabdomere (Bahner et al., 2002). The higher number of TRPL channels in the rhabdomere plasma membrane might correlate with a higher sensitivity of the photoreceptors and would therefore serve the dark adaptation. The structural basis is the presence of TRPL (Bahner et al., 2002). Thr TRPL presence is regulated by both the N- and C-terminus of the TRPL channel protein (Richter et al., 2011). The translocation process appears to involve multiple mechanisms that are ignited by the phototransduction cascade (Meyer et al., 2006). The mediator is Ca^{2+} that enters the cells through TRP channels. The second mechanism is a vesicle bound transportation guided by rab proteins resembling that of rhodopsin distribution (Oberegelsbacher et al., 2011). That also includes the participation of the CULD protein (CUB/LDLa- domain) known for regulation of rhodopsin trafficking in *Drosophila*. Recently, new work added another important protein for the TRPL translocation. Identification and characterization of protein encoded by the ttd14 gene revealed new information about the TRPL trafficking mechanism (Cerny et al., 2015). ttd14 phenotype includes an impairment of TRPL translocation process. In the light, there is a partial inhibition of TRPL removal from the plasma membrane and failure in redistribution

in the dark. The mechanism is not clear but might rely onto binding properties of TTD14 including binding sites for G-proteins and phospholipids. Furthermore, the ttd14 mutant shows retinal degeneration and increased mortality of the larvae so that the TRPL-related phenotype might have explanations that are more complex.

4.5. Summary

The first isolation of a TRP channel gene occurred by investigation of a *Drosophila* mutation. Since then, the analysis of *Drosophila*'s TRP channels generated blueprints for the functional understanding of vertebrate TRP channels in general, especially in retinal neurons and glia cells. Still new impacts into the TRP channel research come from *Drosophila* TRP's. Thus, we gave this chapter a special emphasis.

5. TRP expression in the photoreceptors

Rod and cone photoreceptors are the primary light-sensitive neurons in vertebrate retinas. The tonic release of the neurotransmitter glutamate at bipolar and horizontal cell contacts is controlled by Ca^{2+} influx through non-inactivating voltage-dependent Cav1.4 (L-type) Ca^{2+} channels that act in combination with CICR (release of Ca^{2+} from ryanodine ER stores), mitochondrial sequestration and SOCE (store-operated calcium entry) (Witkovsky et al., 1997; Križaj et al., 1999; Križaj, 2012; Szikra and Križaj, 2009b; Suryanarayanan and Slaughter, 2006; Thoreson, 2021). Rapid, Cav1.4-dependent release predominates at ribbon sites, while non-ribbon sites manifest the slower, ryanodine receptor-dependent component (Chen et al., 2014).

A fascinating aspect of photoreceptor Ca^{2+} homeostasis is the dramatic difference in influx, sequestration, and clearance mechanisms in the primary cilium (OS) and the inner segment (IS)/synaptic compartments. OS $[Ca^{2+}]_i$ reflects balanced activation of CNG channels and NKCX transporters, in contrast to IS/terminal $[Ca^{2+}]_i$ which is maintained by Cav1.4 channels, mitochondrial and ER stores, SOCE and PMCAs (Križaj and Copenhagen, 2002; Križaj, 2005); intersegmental Ca^{2+} diffusion is prevented by the sequestration barrier within ellipsoid mitochondria (Szikra and Križaj, 2007, 2009). Together, influx and clearance pathways maintain $[Ca^{2+}]_i$ within an operating range of 50–700 nM (Sampath et al., 1999; Križaj et al., 2003; Szikra and Križaj, 2006). An interesting challenge, given high-affinity Ca^{2+}clearance mediated by plasma membrane calcium ATPases PMCA1/2 (Križaj and Copenhagen, 1998; Duncan et al., 2006), has been to identify the source of Ca^{2+} influx under light-saturated conditions when both CNG and voltage-operated Ca^{2+} channels are closed yet the hyperpolarized cells maintain a large gradient for Ca^{2+} influx. TRP channels represent potential candidates for this voltage-independent Ca^{2+} influx (Fig. 7).

5.1. TRPC channels in the vertebrate photoreceptors

TRPC1 is the vertebrate homolog of the *Drosophila* TRP gene and the first cloned mammalian TRP gene. Its expression at mRNA and protein levels has been reported in photoreceptors for all species studied so far, including chicken (Crousillac et al., 2003), *Ambystoma* (Szikra et al., 2008), *Xenopus* (Bocchero et al., 2020) and mouse (Gilliam and Wensel 2011; Molnar et al., 2012). Taking into account the usual caveats regarding

TRP antibody labeling (Gilliam and Wensel, 2011; Ryskamp et al., 2015), TRPC1-ir was detected in frog and salamander rod inner segments, terminals and proximal outer segments, and cone terminals additionally labeled with a TRPC6 antibody (Szikra et al., 2008; Bocchero et al., 2020). In light-saturated cells, voltage-operated Ca^{2+} channels are closed, and ER stores are largely emptied of Ca^{2+} (Križaj et al., 2003) while powerful high-affinity PMCA and SERCA pumps continue with the clearance of free Ca^{2+} from the cytosol (Križaj and Copenhagen, 1998; Duncan et al., 2006). To maintain Ca^{2+}-dependent folding, modification and sorting of newly synthesized proteins and protect the cells from ER stress, the cellular machinery requires maintained access to calcium ions. TRPC may subserve this role in combination with Orai channels. Pharmacological experiments in amphibian photoreceptors implicated TRPC1 in store-operated Ca^{2+} entry (SOCE) and maintenance of baseline calcium levels in inner segments of light-saturated cells (Szikra et al., 2008, 2009). Hence, TRPC1 activation could plausibly counterbalance cytosolic $[Ca^{2+}]_i$ decreases caused by prolonged saturation of the phototransduction cascade. We and others also found that ryanodine stores and TRPCs in amphibian rods and cones contribute to neurotransmission under certain conditions (Suryanarayanan and Slaughter, 2006; Szikra et al., 2008, 2009; Chen et al., 2014). While TRPC channels may modulate calcium signaling in all photoreceptor compartments in amphibians, this does not seem to be the case in mammalian rods and cones. *Trpc1* and *Trpc3* genes are strongly expressed in the mouse outer nuclear layer, yet their ablation did not affect scotopic and photopic ERG b-waves. We interepret this result as indicating that TRPC1 and TRPC3 channels do not contribute to phototransduction and kinetics of the light response in mouse rods (Molnar et al., 2012). It remains to be determined whether TRPCs directly interact with Orai channels and the STIM1 depletion sensors and whether activation of TRPC1 relies on the presence of functional Orai channels.

5.2. TRPML channels in the vertebrate photoreceptors

With *in situ* hybridization experiments TRPML1 (also known as MCOLN1) a member of the mucolipin subfamily was detected in photoreceptors as another member of the TRP channels (Gilliam and Wensel 2011). Mutations in TRPML1 cause mucolipidosis type IV (Sun et al., 2000), a neurodegenerative disorder with severe clinical manifestations (Goldin et al., 2008; Venugopal et al., 2007). The $TRPML1^{-/-}$ knock out mouse displays prominent thinning of the photoreceptor layer, suggesting a role for TRPML, a lysosomal protein, in postnatal development of photoreceptors (Grischuk et al., 2016). In a rat model of retinal degeneration caused by retinal detachment the subretinal injection of the TRPML1 agonist ML-SA1 attenuated photoreceptor degeneration, possibly due to reduction in the production of reactive oxygen species (Yan et al., 2021). As intracellular channels located to late endosomes and lysosomes (Venkatachalam et al., 2006), TRPML1 may participate in redox signaling. It should be mentioned that other studies provide evidence that the retinal degeneration caused by TRPML1 mutations may be attributed to a possible localization of the channel to lysosomes of the retinal pigment epithelium (Coblentz et al., 2013; Gómez et al., 2018).

5.3. TRPV channels in the vertebrate photoreceptors

A fascinating recent study has implicated TRPC1 (and Piezo) channels in the regulation of the frog rod photoresponse and in mechanical and light-induced OS deformations (Bocchero et al., 2020). Calcium imaging and whole-cell recording suggest that TRP channels (predominantly TRPC1, TRPV4 and possibly TRPV2) contribute to Ca^{2+} influx into amphibian (salamander, frog) photoreceptor OSs (Bocchero et al., 2020; Pang et al., 2021; Lapajne et al., 2022). Their function may include regulation of retinomotor movements and potentially phototransduction. Salamander (*Ambystoma tigrinum*) rod OSs indeed show temperature-, hypotonicity- and pressure-evoked inward currents (Pang et al., 2021) and respond to TRPV4 agonists with $[Ca^{2+}]_i$ elevations (Lapajne et al., 2022). In addition, immunohistochemistry showed expression of TRPV1 and TRPV2 members of the vanilloid subfamily in synaptic terminals and outer segments of photoreceptors in goldfish and zebrafish retinas (Zimov and Yazulla 2004).

5.4. Summary

TRP channel expression in invertebrate, teleost, amphibian and mammalian photoreceptors shows substantial differences in the type of expressed subtype, and channel localization. A good example is TRPC1 – its fruit fly homolog mediates phototransduction; TRPC1 was suggested to mediate mechanotransduction and store-operated signals in amphibians and the channel is strongly expressed in mouse rods (Molnar et al., 2012) but without known function.

6. TRP channel expression in RGCs

Retinal ganglion cells (RGCs) are projection neurons that transfer visual information from the retina to at least 50 midbrain areas (Martersteck et al., 2017). The >30 types of RGCs have distinct patterns of dendritic stratification, excitatory/inhibitory input, rod/cone input, and axonal projections. Their output integrates glutamatergic (AMPA- and NMDA receptor-mediated) inputs from presynaptic bipolar cells, inhibition by amacrine (glycinergic and GABAergic) cells and their modulation by dopaminergic, purinergic, and peptidergic retinal circuits. RGCs appear uniquely sensitive to mechanical stressors, with modest (3–5 mm Hg) increases in IOP sufficient to dramatically impact RGC firing and survival (Grüsser et al., 1989; Della Santina et al., 2013; El-Danaf and Huberman, 2015). Chronic IOP elevations, prolonged hypoxia, and inflammatory stress increase the risk of neurodegeneration and blindness by injuring RGCs (Almasieh et al., 2012; Križaj, 2019). Literature shows disagreements concerning the functional subpopulations affected by mechanical stress, yet it has become clear that even brief periods of ocular hypertension are sufficient to result in dose-dependent pruning of dendrites and apoptosis (Della Santina et al., 2013; Ou et al., 2016; Feng et al., 2013; El-Danaf and Huberman, 2015; Risner et al., 2018). RGC excitability can be time-dependently enhanced (Risner et al., 2018) or suppressed (Della Santina et al., 2013) by mechanical stress. The unique sensitivity to IOP, chemical and temperature inputs suggests that the cells express transducer molecules that are absent or minimally expressed in other retinal neurons. TRP subunits that are known to be important in neuronal sensing of touch, pain, temperature, osmolarity, pheromones, and taste, such as TRPV4, are indeed strongly expressed in RGCs (Gilliam and Wensel, 2011; Jo et al., 2017)

(Figs. 9 and 10) and have been linked to light-independent sensory transduction (Ryskamp et al., 2011; Križaj, 2016; Jo et al., 2017; Lakk et al., 2017). TRP channel-mediated integration of synaptic and intrinsic light responses with thermal, chemical, and mechanical inputs (e.g., body temperature, endocannabinoids, IOP and ion gradients) indicates that retinal output reflects an integrated response to multiple types of sensory stimuli (Križaj, 2016; Lapajne et al., 2022).

6.1. Rhabdomeric phototransduction by TRPC6/7 channels

One of the most exciting developments in retinal biology over the past two decades has been elucidating molecular pathways that mediate light-evoked signaling in intrinsically photosensitive RGCs (ipRGCs). A landmark study from King Wai Yau's group (Xue et al., 2011) conclusively identified DAG-sensitive TRPC6 and TRPC7 channels as obligatory mediators of the light-evoked current downstream from melanopsin, a light-sensitive rhabdomeric (R-)opsin. A first clue was obtained in a study in which melanopsin, co-expressed with TRPC3, impelled light sensitivity to HEK293 cells (Melyan et al., 2005). The observation suggested that DAG-sensitive TRP channels mediating the light response in fruit fly photoreceptors might contribute to mammalian vision as transducers of the ipRGC light response. Consistent with this, *Trp* transcript analyses in purified cell preparations (Hartwick et al., 2007) and immunohistochemical studies localized multiple TRPC signals to the mouse IPL and ipRGCs (Warren et al., 2006; Sekaran et al., 2007; Witkovsky et al., 2008) but identification of the transducer was confounded by the absence of phenotypes in TRPC3$^{-/-}$ and TRPC7$^{-/-}$ mice, questionable antibody selectivity and reduced but not absent, light responses in TRPC6$^{-/-}$ cells (Gilliam and Wensel, 2011; Perez-Leighton et al., 2011). The issue was resolved by Xue et al. (2011), who reported that the light response is obliterated in double KO (TRPC6/7$^{-/-}$) ipRGCs. It is now clear that light-evoked excitation in mouse ipRGCs reflects cation influx through heteromultimeric channels composed of (interchangeable) TRPC6 and TRPC7 subunits.

A detailed overview of ipRGC phototransduction models is beyond the scope of this review. Still, it is worth noting that rodent ipRGCs include at least 6 classes that comprise 3% of the total RGC population and have been categorized based on process stratification, projection, melanopsin expression, cell body size and receptor fields into M1-M6 subpopulations (Contreras et al., 2021) whereas the human transcriptome so far seems to be limited to a single, M1-like, population (Mure, 2021). TRPC6/7 transduction characterizes light-evoked signaling in mouse M1 cells, Brnb3-negative cells that stratify in the OFF sublamina and project to non-image-forming regions of the visual system associated with circadian photoentrainment, sleep induction and the pupillary reflex (Xue et al., 2011; Sonoda et al., 2018). M1 cells are the only RGC type with high levels of *Trpc6/7* expression (Tran et al., 2019). Neonatal mice lacking TRPC6/7 show reduced photosensitivity in M1 but not other subtypes of RGCs and fail to show photoaversion (Caval-Holme et al., 2022). The M1 population thus appears to constitute a separate information channel for transferring information from the retina to the midbrain. Similar to the *Drosophila* phototransduction pathway described in Section 6, the ipRGC signaling cascade involves R-opsin, transactivation of a $G_{q/11}$ -like protein, PLCβ4 -mediated hydrolysis of membrane phosphatidylinositol-4,5-bisphosphate (PIP_2), and generation of inositol-1,4,5-trisphosphate

(IP_3) and diacylglycerol (DAG) lipid messengers (Fig. 8). M1 TRPC6/7 channels are probably gated via PIP_2 hydrolysis (Itsuki et al., 2014) downstream from $G\alpha_q$, $G\alpha_{11}$, or $G\alpha_{14}$ (Xue et al., 2011; Hughes et al., 2015; Jiang et al., 2018). Consistent with this, the ipRGCs light response is potentiated by membrane-permeant analogs of DAG that activate TRPC3/6/7 channels (Warren et al., 2006, but see Graham et al., 2008).

M2 ipRGCs stratify in the ON sublamina, project to SCN and LGN, and utilize HCN (hyperpolarization-activated cyclic nucleotide-gated) channels in parallel with the TRPC6/7 rhabdomeric pathway for the light response (Jiang et al., 2018). Cyclic nucleotide-dependent signaling in these cells appears independent from *PLCβ1-4*$^{-/-}$ and is insensitive to Ruthenium Red, a nonselective TRP blocker. How PLCβ1-4-dependent TRPC mechanisms interact with *PLCβ1-4*-independent pathways in ipRGCs is not well understood.

M4 ipRGCs are monostratified contrast-sensitive cells that form ON αRGC mosaics, project to the LGN and contribute to visual acuity tracking. Similar to M1s, M4 phototransduction relies on a G_q-coupled PLC, which increases the cells' excitability by closing a TASK-like two-pore potassium (K2P) leak conductance (Sonoda et al., 2018) or a HCN conductance (Jiang et al., 2018). The I-V relationship of the light-evoked current becomes more linear in TRPC 3/6/7 KO retinas, which display impaired responsiveness in the presence of bright light (Sonoda et al., 2018). TASK vs. TRPC6/7 signaling might regulate M4 responses under scotopic vs. photopic conditions. To the best of our knowledge, transduction mechanisms and projection pathways in M3, M5, and M6 cells that mediate chromatic opponency (UV-green) and other ipRGC modalities remain unknown, and different transduction pathways may exist across species. There is an ongoing debate concerning the redundancy of PLC, G proteins, K^+ channels, TRPs and intracellular Ca^{2+} store components, and it is unclear whether PIP2 is required for the closing of TRPC6/7 channels as shown in other preparations.

Immunolabeling for TRPC3, TRPC6, and TRPC7 subunits suggests that DAG-sensitive canonical TRPs are expressed across the IPL/RGCL in non-photosensitive classes of RGC and presumably in amacrine cells (Wang et al., 2010; Witkovsky et al., 2008). The channels could play a role in a wide range of molecular contexts that engage $G\alpha_{q/11}$ -coupled receptors but their functions remain to be ascertained.

6.2. TRPV1 signaling, RGC excitability and glaucoma

TRPV1 was among the first TRP channels studied in the retina and remains one of the most widely studied if little understood isoforms in the retinal TRP armamentarium. TRPV1 expression has been reported in teleost (Zimov and Yazulla, 2004; Nisembaum et al., 2022), mouse (Weitlauf et al., 2014; Jo et al., 2017; Lakk et al., 2017; Risner et al., 2020), rat (Nucci et al., 2007; Leonelli et al., 2009; Sappington et al., 2009), vervet monkey (Bouskila et al., 2020, 2021) and human (Sappington et al., 2015) RGCs. Analyses of the effects of TRPV1 agonists and inhibitors and TRPV1$^{-/-}$ phenotypes in *ex vivo* and intact retinas (Ryskamp et al., 2014b) are consistent with an assortment of TRPV1 functions in mammalian RGCs.

TRPV1-expressing neurons in the central mouse RGCL are mostly displaced amacrine cells, with the density of TRPV1-expressing RGCs increasing towards the periphery (Jo et al., 2017). Vervet monkeys show a similar expression pattern to mouse, with the strongest signal observed in the peripheral retina (Bouskila et al., 2020). Ca^{2+} imaging studies in mouse showed capsaicin responsiveness in ~20% of dissociated mouse RGCs (Jo et al., 2017). Similarly, TRPV1-lineage cells in transgenic *Trpv1*^{Cre}:Ai9 and *Trpv1*^{Cre}:AAV^{-}Flex-tdTomato reporter mice exhibited TRPV1 signals in 20–40% of total RGCs (Jo et al., 2017), with ~36% of mouse RGCs that immunolabel for the intermediary filament SMI-32 (i.e., often used as a marker for the alpha ganglion cell subtype that can be recognized by large cell bodies, monostratified dendritic arbors, and fast conducting axons) also expressing TRPV1 (Lakk et al., 2018). Roughly 70% of RGCs immunolabeled for SMI-32 in human retinas express *Trpv1* mRNA (Sappington et al., 2015), indicating the channel is confined to a subpopulation of αRGCs. It remains to be seen whether TRPV1 localization and expression in human RGCs differs from their mouse counterparts, as recently shown for human and rodent corneal epithelial cells (Lapajne et al., 2020). The overall levels of mouse RGC *Trpv1* mRNA compared to cognate *Trpv2, Trpv4,* and *Trpv6* expression are minuscule (Gilliam and Wensel, 2011; Lakk et al., 2018). Nonetheless, capsaicin evokes $[Ca^{2+}]_i$ signals in a significant cohort of RGCs, indicating that biologically meaningful expression is mediated by a low density of channels. Knocking out the *Trpv4* gene does not produce compensatory changes in *Trpv1* expression and does not affect the amplitude or kinetics of TRPV4-evoked signals (Lakk et al., 2018). Thus, TRPV1 does not form an obligatory complex with the more abundant TRPV4 subunit.

Analyses of TRPV1 signaling in mouse αRGCs by the Calkins laboratory (Risner et al., 2020) brought insights into how the channel shapes neuronal excitability, dendritic remodeling and axonal function in a known glaucoma-susceptible RGC subpopulation. Deletion of the *Trpv1* gene reduced the somatic area, dendritic length and complexity of sustained αON and αOFF cells. TRPV1 knockdown did not affect spontaneous activity in ON cells but reduced it in OFF αRGCs (Risner et al., 2020), suggesting involvement of a signaling pathway that is tonically active in the dark. Firing of TRPV1$^{-/-}$ sustained αON-S RGC increased in the presence of light, suggesting that TRPV1 activity suppresses RGC excitation. TRPV1$^{-/-}$ sustained αOFF-S RGCs similarly showed decreased firing (Risner et al., 2020), but it remains unclear whether these responses include non-autonomous contributions from adjacent TRPV1-expressing amacrine and bipolar cells, integration of bipolar inputs in ON vs. OFF sublaminae, or endocannabinoid inputs. ON TRPV1$^{-/-}$ cells from eyes with elevated IOP show increased depolarization and light-evoked spiking due to upregulation of axonal $Na_V1.6$ channels (McGrady et al., 2020). This effect disappeared by 4 weeks of ocular hypertension (Weitlauf et al., 2014). Another interesting TRPV1$^{-/-}$ phenotype involves reduced dendritic pruning and deterioration of IPL synapses in hypertensive (Risner et al., 2021) relative to wild-type retinas (Della Santina et al., 2013; El-Danaf and Huberman, 2015; Feng et al., 2013; Ou et al., 2016). The neuroprotective effect of TRPV1 during mechanical stress was suggested to involve the Akt/mTOR pathway (Sakamoto et al., 2017). In contrast to the somatic anti-excitotoxic effect of TRPV1 deletion, TRPV1$^{-/-}$ optic nerves in mouse glaucoma models showed accelerated degeneration (Ward et al., 2014) together with an increase in the amplitude of the optic

nerve compound action potential (CAP) and augmented expression of voltage-gated Na^+ channels (McGrady et al., 2020). It remains to be seen whether the vulnerability of $TRPV1^{-/-}$ axons reflects axon-intrinsic gain-of-function effects or loss-of-function due to altered signaling in ONH astrocytes, microglia and endothelial cells. It will also be interesting to ascertain the biophysical properties of the TRPV1-mediated current in RGCs, its biological agonists, binding-modulatory partners, targeting into lipid raft domains, and activity-dependent trafficking and potential parallels to cortical counterparts, which were extensively documented to modulate synaptic transmission via presynaptic and postsynaptic modulation (Bialecki et al., 2020).

In contrast to the protective role of TRPV1 in living mice, 1-day exposure of cultured rat RGCs to 70 mm Hg hydrostatic pressure induced apoptosis that was suggested to be driven by TRPV1-mediated Ca^{2+} influx (Sappington et al., 2009, 2015). Use of hydrostatic pressure as a mechanical modulator of biological responses in RGCs and astrocytes has been questioned (Lei et al., 2011; Osborne et al., 2015) and thus the precise mechanism of TRPV1-dependence of RGC apoptosis remains to be ascertained. High-IOP DBA-2J eyes show increased TRPV1-immunoreactivity in RGC dendrites (Sappington et al., 2009), with mechanical stress in RGC cultures associated with ~12-fold increase in *Trpv1* mRNA expression (Sappington et al., 2015). Ischemia-reperfusion (Nucci et al., 2007) and optic nerve transection (Leonelli et al., 2009), in contrast, reduced TRPV1 expression, indicating that the gene is under stringent modulatory control by the external milieu. Cells that overexpress TRPV1 channels generally do not respond to pressure steps with mechanosensitive currents (Nikolaev et al., 2019) and we were unable to discern direct roles for TRPV1 activation in RGCs stimulated with stretch, shrinking, or pressure (Ryskamp et al., 2011; A Jo, O. Yarishkin, and D. K., unpublished data). TRPV1 channels in wild-type mouse RGCs cannot be activated by cell shrinking (Ryskamp et al., 2011; Jo et al., 2017), suggesting that the cells express the full-length protein variant. However, iPSC -derived human RGCs may express the truncated N-terminal variant, as indicated by TRPV1 sensitivity to hyperosmotic stress (Hsu et al., 2019; Zaelzer et al., 2015).

Similar to TRPV4, TRPV1 in RGCs almost certainly behaves as a molecular integrator of chemical, mechanical, heat and nociceptive stimuli that may include sensitivity to noxious (>43 °C) temperature, acid pH, and a wide assortment of lipids - endocannabinoids (“endovanilloids” anandamide (AEA; N-arachidonoylethanolamine) and N-arachidonoyl dopamine, N-oleoyl dopamine)), 2-arachidonoylglycerol (2-AG), arachidonic acid metabolites (12(S)-hydroxyglutaric acid, 12-hydroxyhexanedienic acid and 20-hydroxyeicosatetraenoic acid (20-HETE)), lipoxygenase products, monoacylglycerols and retinoids (Nilius and Szallasi, 2014). Their function may include detection of local inflammation (Marinelli, 2017), regulators of intracellular ion concentration (Miraucourt et al., 2016), synaptic plasticity (Egaña-Huguet et al., 2021) and sensing the local modulatory milieu. RGCs co-express (ionotropic) TRPV1 and (metabotropic) CB1 receptors, which are simultaneously stimulated by activity-dependent release of endocannabinoids anandamide (AEA) and 2-AG (Ryskamp et al., 2014b; Bouchard et al., 2016). AEA elevates $[Ca^{2+}]_i$ directly via TRPV1 activation, whereas 2-AG lowers the amplitude of AEA-induced $[Ca^{2+}]_i$ elevations through CB1R-dependent lowering of $[cAMP]_i$ (Jo et al., 2017). This suggests a sequential mechanism whereby activity-dependent endocannabinoid release within the

bipolar-amacrine-RGC circuit results in transient TRPV1-mediated excitation followed by sustained 2-AG-mediated activation of CB1R- and Gi-dependent pathways (Fig. 9).

Endocannabinoids may simultaneously suppress presynaptic release and stimulate postsynaptic TRPV1 channels (Middleton and Protti, 2011; Middleton et al., 2019; Jo et al., 2017). An investigation of spontaneous RGC firing by Protti's group additionally found that endocannabinoids augment the (amacrine-mediated inhibitory) surround of ON-S RGCs (Middleton et al., 2019), suggesting that endocannabinoids regulate the postsynaptic signal gain through parallel yet independent modulation of receptive field center and surround mechanisms. The calcium-dependent modulation might accentuate contrast sensitivity while preserving the response bandwidth of the bipolar-RGC synapse (Middleton et al., 2019). In addition, analogy with sensory and central neurons (Alessandri-Haber et al., 2009) predicts roles for TRPV1 in adaptive potentiation/suppression of excitatory/inhibitor balance (Egaña-Huguet et al., 2021), inflammatory sensitization that reflects intra-retinal release of prostaglandins, ATP, TNFα, bradykinin and protons. Another intriguing candidate for TRPV1 activation are retinoids that are continually recycled by Müller glia. The vitamin A metabolite 9-cis retinoic acid has been implicated, for example, in TRPV1-dependent induction of neuronal sensitivity and neurogenic inflammation (Yin et al., 2013).

6.3. RGC TRPV4 signaling, volume regulation and pathology

Mouse RGCs show the following vanilloid expression pattern: *Trpv4*>*Trpv2*>*Trpv1* = *Trpv3* (Lakk et al., 2018) (Fig. 10A). TRPV4 expression has been reported in teleost (salmon; Nisembaum et al., 2022), tiger salamander (D. Ryskamp, D. K., unpublished observations), rat (Sappington et al., 2015; Li et al., 2021a,b), pig (Taylor et al., 2017), non-human primate (Gao et al., 2019) and human (Ryskamp et al., 2011) RGCs. In general, expression seems to be strongest in cells with large somata (Ryskamp et al., 2011; Lakk et al., 2018; Gao et al., 2019). TRPV4-ir signals in cell bodies and proximal dendrites are more pronounced compared to distal dendrites (Ryskamp et al., 2011; Lakk et al., 2018) (Fig. 10C), whereas axons are labeled by some but not all TRPV4 antibodies. Consistent with the absence of TRPV4-ir in the distal retina (Ryskamp et al., 2011), global ablation of TRPV4 channels has no effect on retinal ERG a- and b-waves, and shows a minimal effect on oscillatory potentials (Yarishkin et al., 2018). This points at RGCs as the main generators of retinal neuronal TRPV4 activity.

Exposure to TRPV4 agonists such as GSK1016790A (Fig. 10D) and phorbol esters evokes a nonselective inward cationic current, promotes excitability and elevates $[Ca^{2+}]_i$ in rodent and primate RGCs (Ryskamp et al., 2011, 2014; Lakk et al., 2018; Gao et al., 2019). In contrast to sustained TRPV4 activation in non-excitable cells (Jo et al., 2015; Phuong et al., 2016; Lapajne et al., 2020; Redmon et al., 2021), TRPV4 channels in RGCs activate with rapid onset and show significant inactivation/desensitization. The attendant increase in $[Ca^{2+}]_i$ is similarly transient (Ryskamp et al., 2014a; Lakk et al., 2018). The differences in activation between retinal neuronal and glial TRPV4 channels may reflect cell-type-specific engagement of the PLA2-EET cascade and differential roles of Ca^{2+}-dependent inactivation.

Swelling-induced TRPV4 activation in RGCs occurs at $\Delta > 30$ mOsm, suggesting that the RGC TRPV4 channels are not sensitive to osmotic gradients under physiological

conditions. Because the RGC response desensitizes in continuous presence of hypotonic stress (Ryskamp et al., 2011; Lakk et al., 2018; Toft-Bertelsen et al., 2019), TRPV4 channels are unlikely to significantly contribute to cells' volume regulation. Sensitivity to stretch may be augmented during excessive swelling in glaucoma, ischemia and diabetes (Reichenbach and Bringmann, 2010; Pinar-Sueiro et al., 2011).

A hereditary channelopathy caused by missense variants of the TRPV4 gene produces a dominant autosomal phenotype associated with loss of hearing and blindness (Thibodeau et al., 2017). TRPV4 mutations have also been associated with debilitating sensory and motor neuropathies that include hereditary motor and sensory neuropathy type 2C (also known as Cgarcot Marie Tooth type 2C), scapuloperoneal spinal muscular atrophy and congenital distal spinal muscular atrophy (Echaniz-Laguna et al., 2014; Nilius and Szallasi, 2014). It remains to be seen whether high TRPV4 expression in αRGCs (Ryskamp et al., 2011; Lakk et al., 2018) predisposes them to injury from mechanical stress. It is worth noting that TRPV4 agonists induce RGC apoptosis (Ryskamp et al., 2011) whereas TRPV4 inhibition and gene deletion improve neuronal survival in pig (Taylor et al., 2017) and mouse (Matsumoto et al., 2018) models of retinal detachment.

6.4. Open questions regarding TRP isoforms in RGCs

TRPV2.—Analysis of thermoTRP transcripts in mouse RGCs showed relatively abundant *Trpv2* expression (Fig. 9A). Antibody labeling in rodent retinas was inconclusive (Gilliam and Wensel, 2011; Leonelli et al., 2009).

TRPC1.—*In situ* hybridization shows moderate *Trpc1* expression in all nuclear layers of the mouse retina, including RGCL (Molnar et al., 2012).

TRPC5.—TRPC5 may suppress the length of RGC axons in developing retinas, whereas its antagonist clemizole enhances axonal outgrowth (Oda et al., 2020). How the channel is activated under physiological conditions is unknown.

TRPM3.—Antibody staining (Brown et al., 2015), reporter expression (Hughes et al., 2012), and functional assays (Brown et al., 2015) documented TRPM3 expression in a subset of RGCs. Altered pupillary light reflex in TRPM3-null mice under photopic and scotopic conditions (Hughes et al., 2012) predicted expression in ipRGCs yet a TRPM3 promoter-driven reporter did not co-localize with melanopsin (Hughes et al., 2012). Synthetic TRPM3 agonists evoke calcium responses and retinal waves in developing retinas but TRPM3 KO mice have normal ERGs (Brown et al., 2015).

TRPA1 is a redox-sensitive channel activated by the mustard oil component allyl isothiocyanate (AITC) and by intense cooling. It has been localized to RGCs from chick, mouse and human retinas (Araújo et al., 2020). We find that dissociated adult RGCs respond to AITC with large $[Ca^{2+}]_i$ elevations that are comparable to the effects of saturating concentrations of glutamate (Fig. 10). Deletion and pharmacological inhibition of TRPA1 attenuated the increase in the apoptosis biomarker, active caspase-3, reduced retinal cell death and preserved retinal tissue thickness in retinal models of oxidative stress (Araújo et al., 2020) whereas $TRPV1^{-/-}$ and $TRPV4^{-/-}$ retinas showed no difference from controls.

TRPM8.—Literature search shows no studies on TRPM8 channel expression in the retina. Our pilot experiments (A. JO and D.K.) demonstrate that TRPM8-selective agonists such as icillin evoke large calcium signals in a subset of RGCs (Fig. 11).

6.5. Summary: multisensory transduction and thermosensing in RGCs

TRP channels are emerging as important non-synaptic regulators of RGC signaling, survival and output. They regulate cell swelling (TRPV4; Ryskamp et al., 2011, 2014b, 2015; Toft-Bertelsen et al., 2019), response to mechanical stress (TRPC1, TRPV1; TRPV4; Sappington et al., 2009; Molnar et al., 2016), membrane lipids (TRPV1/4; Ryskamp et al., 2014b, 2016), cholesterol (Lakk et al., 2017), endocannabinoids (TRPV1; TRPV4; Jo et al., 2017); Ca^{2+} store repletion (TRPC1, TRPC6; Da Silva et al., 2008; Szikra et al., 2009; Molnar et al., 2016) and transduction of the ipRGC light response (TRPC6/7; Xue et al., 2011). It is unclear to which extent TRP subunits heteromerize to form functional channels. For example, ~10% of RGCs coexpress TRPV1 and TRPV4 subunits (Lakk et al., 2018), and Sappington et al. (2015) showed that TRPV4 antibodies co-immunoprecipitate TRPV1 in a rat RGC preparation (Sappington et al., 2015). Several TRPs, including TRPV1-4, A1, C6, and M3 may sensitize RGCs to pathological stressors whereas others (TRPC1, TRPV1) might be protective in other contexts (Molnar et al., 2016; Risner et al., 2020). Although the retina is isothermic and not expected to experience thermal shifts, it is remarkable that RGCs express most if not all “thermoTRP” channels that cover the spectrum of temperature activations from <10 °C (TRPA1) to > 40 °C (TRPV1, TRPV2) (Fig. 10). Transcriptionwise, the dominant channel is TRPV4, with the activation optimum around the body temperature (Jo et al., 2017), with the overall pattern of transcription similar to dorsal root and trigeminal ganglion neurons in which thermoTRP channels engage in multiple modes of sensory transduction (Clapham, 2003).

7. TRPM channels in retinal bipolar cells

Two TRPM subunits with reliable detection in mammalian retinas are TRPM1 and TRPM3 (Brown et al., 2015; Gilliam and Wensel, 2011; Ribelayga et al., 2010). TRPM3 locates to the inner plexiform layer, close to OFF system synapses. The ERG b-wave of *Trpm3*$^{-/-}$ mice is normal, supporting a role for ganglion cell function (Brownet al., 2015). In contrast, analysis of TRPM1 in the retina has led to a quantum jump in our understanding of visual information processing (Almutairi et al., 2021; Koike et al., 2010a; Oancea and Wicks, 2011). The TRPM1 gene produces two isoforms, TRPM1-L (long form = full-length protein predicted from the gene) and TRPM-S (short form = N-terminal truncated form) (Duncan et al., 1998; Fang and Setaluri, 2000; Koike et al., 2010b). TRPM1-S localizes to the inner plexiform layers and during embryonic development to the RPE. All known TRPM1 splicing variants can produce ionic currents including TRPM1-S (Oancea et al., 2009) and presumably contribute to the membrane conductance in these structures. The ion channel encoded by TRPM1-L is expressed by ON bipolar cells and responsible for the signal inversion from light-induced hyperpolarization of photoreceptors into depolarization of ON bipolar cells.

7.1. TRPM1 channels and an old problem in bipolar cell functions

Vision starts with light-dependent activation of photoreceptors. Parallel processing by the neuronal network that is activated by photoreceptors identifies essential elements of visual information such as color, shape or movements (Boycott and Wassle, 1999; Wassle, 2004; Wassle and Boycott, 1991). The parallel processing starts with the bipolar cells, which consists of two basic functional types, the ON and the OFF cells. ON bipolar cells mediate the light signal by depolarizing in response to glutamate released from photoreceptors. TRPM1 was identified as the ON bipolar transduction channel following a pioneering study of the spotting coat pattern in Appaloosa horses (Bellone et al., 2008; Koike et al., 2010a; Schneider et al., 2015). Expression of the TRPM1 channel in melanocytes determines the coat pattern in these animals (Devi et al., 2013; Guo et al., 2012; Hwang et al., 2016; Jia et al., 2020).

Bellone et al. (2008) noted that the horses suffer from congenital stationary night-blindness, sparking investigations by several research groups in retinas across species. They localized the TRPM1 channel to ON bipolar cells. (Gilliam and Wensel, 2011; Klooster et al., 2011; Koike et al., 2010a, 2010b; Morgans et al., 2009, 2010). Heterologous expression of TRPM1 reveals that this is a non-selective cation channel that conducts Ca^{2+}, shows a double rectification in current-voltage plots and leads to cell depolarization (Koike et al., 2010b; Lambert et al., 2011; Oancea et al., 2009). TRPM1 deficient mice showed a no-b-wave phenotype in the scotopic ERG (Koike et al., 2010b; Morgans et al., 2009; Shen et al., 2009) together with an intact a-wave response (rod activation) and loss of transduction currents in ON- but not OFF bipolar cells (Koike et al., 2010b; Morgans et al., 2009). Genetic analyses in humans revealed that mutations in the TRPM1 gene represents a primary cause for the complete form of CSNB1 (Almutairi et al., 2021; Audo et al., 2009; Li et al., 2009; Malaichamy et al., 2014; Nakamura et al., 2010; van Genderen et al., 2009; Zeitz et al., 2015). Thus, the TRPM1 channel in ON bipolar cells mediates the long-sought mechanism that translates light-dependent rod hyperpolarization into ON excitation.

7.2. Mechanisms of TRPM1 activation by glutamate receptor deactivation

Subcellular localization analysis of TRPM1 in bipolar cells provided the first clues into the underlying signaling cascade that drives the light-dependent ON bipolar depolarization. TRPM1 co-localizes with the Gαo, G-protein regulators the metabotropic glutamate receptor mGluR6 in bipolar dendritic tips (Cao et al., 2009; Dhingra et al., 2008; Klooster et al., 2013; Koike et al., 2010a, 2010b; Križaj et al., 2010; Morgans et al., 2010). Localization requires rod photoreceptor activity (Križaj et al., 2010). TRPM1 expression and localization in mice take place following the eye opening. Three papers from Scott Nawy implicated a non-selective CNG cation channel in mGluR6-dependent activation of Gαo (Nawy, 1999; Nawy and Jahr, 1990, 1991). mGluR6, RGS7 (regulator of G protein signaling 7) or RGS11 deficient mice also show loss or reductions in the scotopic b-wave (Cao et al., 2012; Chen et al., 2010; Koyasu et al., 2008; Mojumder et al., 2009; Shim et al., 2012). A hypothetic final pathway could be developed via heterologous expression experiments using CHO or HEK293 cells as an expression system. Heterologous expression of TRPM1 leads to small currents so the deeper biophysical/electrophysiological characterization of TRPM1 was possible but difficult (Koike et al., 2010b; Lambert et al., 2011; Oancea et al., 2009;

Shen et al., 2012). The group of Oberwinkler (Lambert et al., 2011) found an approach to record currents from the TRPM1 gene product heterologous expression strong enough for biophysical analysis. The group found that exon 11 in the TRPM1 gene is not present in the TRPM3 gene, which shows normally robust current in heterologous expression. Lambert et al. (2011) removed exon 11 from the TRPM1 gene and could measure currents from this gene product that permitted an electrophysiological and pharmacologic characterization. The group of Furukawa (Koike et al., 2010b) mimicked the situation of signaling proteins in CHO cells via heterologous expression of TRPM1L, mGluR6. Koike et al. al (Koike et al., 2010b). showed suppression of TRPM1 currents by glutamate via a Gαo-dependent mechanism. Finally, the group showed in inside-out patch recordings a decrease in the TRPM1 single-channelopen probability when purified Gαo protein was applied from the intracellular side of the membrane patch (Koike et al., 2010a, 2010b). Thus, a possible signal cascade in ON bipolar might look as follows: the light-dependent depolarization of ON bipolar cells occurs by deactivation of mGluR6 receptor and subsequent reduction in the number active Gαo proteins that are suppressors of the TRPM1 channel.

The above constructed model for the signaling cascade bases onto data from heterologous expression systems, from expression in cell types that are not neurons. The question is whether this model applies also to the *in vivo* situation of bipolar cells. Both mGluR6 and the TRPM1 knockout show loss of the ERG b-wave (Koike et al., 2010b; Koyasu et al., 2008; Morgans et al., 2009). Electrophysiological recordings from ON bipolar cells revealed that the loss of b-wave is caused by the inability of these cells to react with hyperpolarization (Koike et al., 2010b; Morgans et al., 2009). The role of G protein-dependent signaling is also substantiated by the RGS7 and RGS11 knockout models (Cao et al., 2009, 2012; Chen et al., 2010; Shim et al., 2012). The reduction of ERG b-waves but also reduced ON bipolar activity in single cell recordings generated a consistent picture of the role of G protein signaling in light-dependent depolarization of ON bipolar cells. RGS7 and/or RGS11 knockout phenotypes are more complex than those of TRPM1 and mGluR6 deficient mice. The b-waves are not fully absent but are reduced or delayed, possibly involving compensatory upregulation. At the far end is the inhibition of TRPM1 by G protein subunits. ON bipolar cells of Gαo knockout mice show absent glutamate induced currents (Dhingra et al., 2000; Okawa et al., 2010). Okawa et al. (2010) used knockout mouse models of splice variants of the Gαo proteins: Gαo1 and Gαo2. The group recorded single flash responses from ON bipolar cells and found that deletion of a single splice variant did not disrupt the ON bipolar response but seem to regulate the ON bipolar cell's sensitivity to light stimuli. The study by Dhingra et al. (2002) investigated the two Gαo splice variants in specific knockout models at the level of single flash Ganzfeld ERG and concluded that only Gαo1 is the critical mediator for the ON bipolar light response. However, it is to mention that Dhingra et al. used only three light intensities, one scotopic, one mesopic and one photopic response. So, the authors did not analyze the luminance response curve that might have provided information about the sensitivity of the b-wave response. Furthermore, the a-wave response in the mesopic response was smaller, indicating effect of the Gαo1 knockout at the photoreceptor level. Shen et al. showed that intracellular dialysis of ON bipolar cells with Gβ1γ2 dimers reduced the TRPM1 currents (Shen et al., 2012). Using transgenic approaches that enable a valid ON bipolar cell identification

by GFP showed that ON bipolar cells display a specific expression of Gβ and Gγ protein expression: Gβ3, Gβ4 and Gγ13 (Dhingra et al., 2008; Huang et al., 2003). Indeed, a Gγ13 knockout mouse displays a reduced b-wave (Ramakrishnan et al., 2015). This group also concluded by co-localization experiments that the combination of Gβ3γ13 is the primary Gβγ dimer in the light signaling cascade in ON bipolar cells.

7.3. TRPM1 forms a signaling complex in ON bipolar cells

With more genes identified that lead to congenital stationary night blindness new properties of TRPM1 channels in ON bipolar cells appeared. These properties would permit a better understanding of the mechanisms that lead to congenital stationary night blindness and would integrate the function of the products of genes that are mutated in disease. Surprisingly, these data lead to conlcusoin that the TRPM1 signaling pathway is arranged in a signaling complex that resembles to the one known in *Drosophila* photoreceptors. The protein that has permitted a new insight is nyctalopin. Mutations in the nyctalopin coding gene cause congenital stationary night blindness (Bech-Hansen et al., 2000; Zeitz et al., 2003). Nyctalopin is expressed in ON bipolar cells (Morgans et al., 2006; O'Connor et al., 2005). Co-immunoprecipitation experiments showed that TRPM1, mGluR6 and nyctalopin are parts of a signaling complex in ON bipolar cells (Cao et al., 2011; Pearring et al., 2011). Via the binding nyctalopin anchors this complex to the plasma membrane either by a transmembrane region (rodents) or by a GPI anchor (O'Connor et al., 2005; Zeitz et al., 2003). mGluR6 itself forms complexes with a transmembrane G protein-coupled receptor GPR179 (Orlandi et al., 2013, 2018); a receptor with so far unknown ligand that is required for the ON bipolar cell light response and its gene can cause stationary night blindness (Klooster et al., 2013; Peachey et al., 2012). More important for the TRPM1 activity is the ability of GPR179 also to form complexes with RGS7 and RGS11 that modulate the light transduction cascade in ON bipolar cells. As GPR179 might regulate the mGluR6 sensitivity (Klooster et al., 2013) it might modulate the G protein dependent inhibition of TRPM1.

7.4. Summary and open questions

Negative regulation of TRPM1 generates the light response of ON bipolar cells. The unsolved issues include the need to characterize TRPM1 channel properties: pharmacology, potential multimeric channel proteins and the confounding issue of the effects of TRPV1 modulators. The antagonist capsazepine blocked both capsaicin- and glutamate- elicited cation conductance of ON bipolar cells yet TRPV1 knockout mice show normal ERG (Shen et al., 2009). Heterologously expressed TRPM1 channels were unaffected by capsaicin but inhibited by capsazepine (Lambert et al., 2011; Schneider et al., 2015). The difference between native TRPM1 and heterologously expressed channels was ascribed to the unique protein environment in ON bipolar cells (Lambert et al., 2011; Schneider et al., 2015). In contrast to other TRPM channels, TRPM1 lacks an amino acid sequence that permits formation of homotetramers (Agosto et al., 2014; Tsuruda et al., 2006).

The interaction between the G protein and TRPM1 is under debate. Gαo knockdown abolished the b-wave and ON bipolar light response (Dhingra et al., 2000, 2002; Okawa et al., 2010) and intracellular application of Gαo in ON bipolar cells demonstrated the inhibition of bipolar cell cation current (Nawy, 1999). However, expression profiles and

heterologous expression suggest that the Gβγ dimer may have similar function to Gαo (Ramakrishnan et al., 2015; Shen et al., 2012). Xu et al. (2016) showed that Gαo and the Gβ3γ13 dimer bind to TRPM1 to synergistically modulate TRPM1 activity. Identification of the G protein binding domain might resolve the issue.

Another novel mechanism involves protein kinase Cα (PKCα) modulation. ON bipolar cells are the retina's only cell type expressing PKCα (Ruether et al., 2010; Xiong et al., 2015). PKCα knockout mice show comparable b-wave amplitudes to wild-type mice, however, the b-wave is characterized by delayed rise-time and decay (Ruether et al., 2010; Xiong et al., 2015). PKCα is thus likely to enhance the ON bipolar light response, possibly by relieving the Mg^{2+} block of TRPM1 (Rampino and Nawy, 2011). Another unexplored mechanism involves protein kinase Cα (PKCα) modulation. ON bipolar cells are the only cell type in the retina that expresses PKCα (Ruether et al., 2010; Xiong et al., 2015). PKCα knockout mice show comparable b-wave amplitudes to wildtype mice, however, the b-wave is characterized by delayed rise-time and decay (Ruether et al., 2010; Xiong et al., 2015). PKCα is thus likely to enhance the ON bipolar cell light response, possibly by relieving the Mg^{2+} block of TRPM1 (Rampino and Nawy, 2011).

8. TRP expression in horizontal and amacrine cells

Horizontal and amacrine cells are responsible for the initial signal processing within the retina. Through feed-back (cone - horizontal cell – cone - bipolar cell) and feed-forward inhibition (cone -horizontal cell – bipolar cell) at the first synapse, horizontal cells influence the activity of photoreceptors and bipolar cells. The feedback inhibition is mediated by either acidification of the synaptic cleft, or the ephaptic influence of connexins. Bipolar cells may be inhibited by GABA release from horizontal cells through GABAC receptors. The role of TRP channels is almost entirely unknown. There have been no functional studies, with antibody labeling suggesting potential TRPV1 expression in monkey horizontal cells (Bouskila et al., 2020).

Amacrine cells have been categorized, depending on the species, into 23 to 63 subtypes (Shekhar and Sanes 2021). Accordingly, they were proposed to fulfill a range of different functions. A systematic screen of TRP channels in the mouse retina attributed a positive signal for TRPC5 to amacrine cells (Gilliam and Wensel 2011). Various TRPC subunits were identified in primary cultures and retina slices from chicken (Sosa et al., 2002; Crousillac et al., 2003; Maddox et al., 2018). These have been implicated in NO dependent GABA release by amacrine cells (Maddox et al., 2018). Analysis of transgenic TRPV1-tdT retinas shows ubiquitous TRPV1 expression in regular and displaced mouse amacrine cells (Jo et al., 2017). Overall, the data concerning the involvement of TRP channels in both horizontal and amacrine cells appear to be sparse yet a substantial role for TRP channels in amacrine signaling seems likely and we suggest that further investigation of TRP channel signaling in horizontal and amacrine cells would be of considerable benefit for the understanding of retinal signal processing.

9. Summary: the multimodal potential of TRP channels in retinal research

Multimodal activation of TRP channels represents a gateway to understanding how the retina integrates light-evoked and light-independent information. TRP channel research has generated breakthroughs in understanding key retinal and biological functions such as circadian photoentrainment, non-image-forming vision, pupillary light reflex, ON bipolar transmission, mechanotransduction, and regulation of retinal barriers (Fig. 12). Multimodality of TRP channel activation undergirds signaling pathways that drive pathological remodeling in glaucoma, diabetes, macular degeneration, mucolipidosis together with reactive gliosis, remodeling of retinal circuits and altered outer/inner barrier permeability. Understanding these mechanisms will aid the development of conceptual and translational strategies to restore vision by targeting specific TRP isoforms. This will take investment and time. TRP channels in the fruit fly rhabdomere were the first TRP with a defined function, yet it took more than 15 years to gain insight into their activation mechanism, which continues to be investigated to this day. Many questions remain regarding the signal transduction mechanism in different types of ipRGC, rod bipolar cells, cone ON bipolar cells, and the role of TRPs in biomechanical milieu sensing by Müller glia, microglia, retinal and optic nerve head astrocytes, RPE and endothelial cells. We note that the biological functions of the large majority of known TRP channels in the retina and the eye remain to be explored and defined. The biology of retinal TRP channels is thus likely to remain a productive area of research for years to come.

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Data availability

Data will be made available on request.

Abbreviations

AAV	adeno-associated virus
2-AG 2	arachidonoylglycerol
2- APB	2-aminoethoxydiphenyl borate
AEA	endocannabinoids anandamide
AKT	a serine/threonine protein kinase = protein kinase B
AMPA	aminomethylphosphonic acid
ANK	ankyrin
AQP	aquaporin

ARPE19	RPE cell line
AT1	angiotensin-2 receptor type 1
ATRAP	angiotensin-receptor associated protein ATP adenosine triphosphate
BAPTA	1,2-bis(o-aminophenoxy)ethane-N,N,N′,N'-tetraacetic acid = Ca^{2+} chelator BRB blood retina barrier
C3a, C5a	complement reaction products - anaphylatoxins
CaM	calmodulin
CaMKII	calmodulin kinase II
CAP	optic nerve compound action potential
CB1R	cannabinoid receptor 1
CHO	Chinese hamster ovary cells
cGMP	cyclic guanosine monophosphate
CICR	Ca^{2+}-induced Ca^{2+} release
CNG	cyclic nucleotide gated
CNS	central nervous system
CRAC	Ca^{2+} release-activated channel
CRAC/CARC	cholesterol recognition/interaction amino acid consensus
CULD	C1r/C1s, Uegf, Bmp1 domain/Low Density Lipoprotein Receptor Class A domain
CYP450	cytochrome P450
DAG	diacyl glycerol
ECM	extracellular matrix
EET	epoxygenase-derived eicosanoids
ERG	electroretinogram
Fura-2	Ca^{2+}-sensitive fluorescence dye
GABA	γ-Aminobutyric acid
GFAP	green fluorescent protein
GPCR	G protein coupled receptor
GPR179	G protein coupled receptor 179

HCN	channel hyperpolarization-activated cyclic nucleotide-gated cation channel
HEK293	human embryonic kidney cells 293
HETE	hydroxyeicosatetraenoic acids
HMGB1	high-mobility-group-protein B1
IGF-1	insulin-like growth factor-1
IL-1, -6, -8	interleukin-1, -6, -8
ILM	inner limiting membrane
inaC	inactivation no afterpotential C
inaD	inactivation no afterpotential D
InsP3	inositol-1,4,5-trisphosphate
IOP	intraocular pressure
IPL	inner plexiform layer
ipRGC	intrinsically photosensitive retinal ganglion cell JAK2 Janus kinase 2
Kv2.1; 8.2	voltage-gated K^+ channel 2.1 or 8.2
LCN	lateral cerebellar nucleus
LGN	lateral geniculate nucleus
LIC	light activated current
L-type	low voltage-activated, long lasting Ca^{2+} channel subtype
MβCD	methyl-β-cyclodextrin
MCP1	monocyte chemoattractive protein-1
mGluR1, 6	metabotropic glutamate receptor-1, -6
ninaE	neither inactivation nor afterpotential
E mTOR	mammalian Target of Rapamycin
NKCX	Na^+,K^+-Ca^{2+} exchanger
NMDA	N-methyl-D-aspartate
$NMDG^+$	N-methyl-D-glucamine
NO	nitrogen mono oxide
norpA	no receptor potential A

OLM	outer limiting membrane
OPL	outer plexiform layer
QMMuC1	Müller cell line
PACSIN	3 protein kinase C and casein kinase II substrate
PAR2	protease-activated receptor 2
PDZ	post-synaptic density protein 95, disc large tumor suppressor 1, zona occludens1
PI3-kinase	phosphoinositide-3-kinase
PIP2	phosphatidylinositol-4,5-bisphosphate
PKC	proteinkinase C
PLA2	phospholipase-A2
PLC	phospholipase C
PLCβ4	phospholipase Cβ4
PMCA	plasma membrane Ca^{2+} ATPase
PNS	peripheral nervous system
PUFA	poly-unsaturated fatty acids
rdgA	retinal degeneration A
rdgC	retinal degeneration C
RGC	retinal ganglion cell
RGS7, 11	regulator of G-protein signaling 7, 11
RPE	retinal pigment epithelium
RT-PCR	reverse transcription polymerase chain reaction
RVD	regulatory volume decrease
SCN	suprachiasmatic nucleus
SERCA	sarcoplasmic Ca^{2+} ATPase
SOCE	store-operated Ca^{2+} entry
SNP	single-nucleotide polymorphism
STAT	signal transducers and activators of transcription
STZ	streptozocin

STIM1	stromal interaction molecule 1
TASK	tandem pore domain K^+ channels
TNFα	tumor necrosis factor alpha
TRP	transient receptor potential
TRPC	canonical transient receptor potential channel
TRPL	L-subtype of Drosophila's TRP channel
TRPM	melastatin subtype of transient receptor potential channel
TRPN	transient receptor potential channel/nompC subtype
TRPP	polycystin subtype of transient receptor potential channel
TRPV	vanilloid-subtype of transient receptor potential channel
ttd14	GTP- and phospholipid-binding protein
VEGF-A	vascular endothelial growth factor-A

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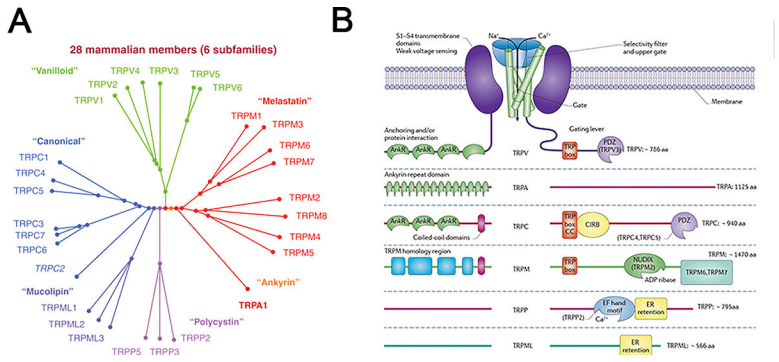

Fig. 1. Phylogenetic tree of the mammalian TRP family

(A) TRPC (canonical), TRPV (vanilloid), TRPM (melastatin), TRPA (ankyrin), TRPML (mucolipin), TRPP (polycystin) (Gees et al., 2014). **(B)** Subunit-specific organization of amino acid domains. TRPC, TRPV and TRPA possess N-terminal ankyrin repeat domains. TRPC, TRPM and TRPV contain the “TRP box” believed to modulate gating. TRPP and TRPML have endoplasmic reticulum (ER) retention domains. CIRB, calmodulin/inositol-1,4,5-trisphosphate (Ins(1,4,5)P3) receptor binding domain; NUDIX, nucleoside diphosphate-linked moiety X; PDZ, acronym for postsynaptic density protein 95 (PSD95), Drosophila disc large tumour suppressor (DLGA) and zonula occludens protein 1 (ZO1). from Moran et al. (2011), and Gees et al. (2014).

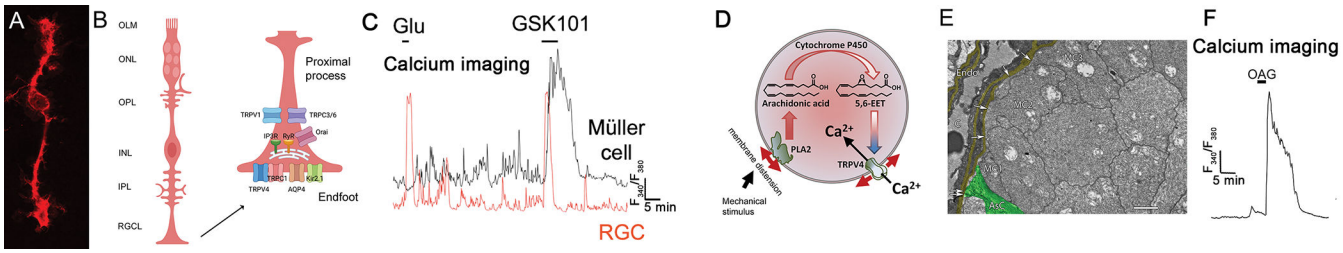

Fig. 2. TRP and Müller cell function.

(A) Dissociated mouse Müller cell labeled with an anti-glutamine synthetase antibody. **(B)** Schematic representation of a generic Müller cell, with apical microvilli within the outer limiting membrane (OLM), lateral processes in the OPL and IPL, INL cell body and the endfoot in the RGCL, abutting the ILM. The inset expands the endfoot region, with strong expression of TRPV4 and TRPC1 in the proximity to ER cisternae containing inositol triphosphate receptors (IP3R) and ryanodine receptors (RyR). Coupling between TRPV4, TRPC1, Orai and store release (RyR, IPR3) channels underlies TRP-dependent Calcium-Induced Calcium Release and Store-operated Calcium Entry mechanisms that contribute to glial excitation. Coupling between TRPV4, inwardly rectifying potassium (Kir2.1) channels and bidirectional water transport across aquaporin (AQP4) channels mediates cell swelling and volume regulation. TRPC3, TRPC6 and TRPV1 channels are probably localized to Müller glial soma and processes, with expression in the endfoot remaining unclear. **(C)** Calcium imaging. Simultaneous recording from a mouse Müller cell and ganglion cell loaded with the calcium indicator dye Fura-2 AM. The TRPV4 agonist GSK1016790A (GSK101), but not glutamate (Glu), evokes a slow and sustained $[Ca^{2+}]_i$ elevation in the glia whereas the RGC responds GSK101 with a rapid inactivating $[Ca^{2+}]_i$ signal, and is also excited by glutamate. **(D)** Possible mechanism of TRPV4 activation in glia. Ca^{2+} influx via TRPV4 stimulates membrane phospholipase A2 (PLA2), which may also be sensitive to lipid distension. PLA2-dependent cleavage of membrane lipids generates arachidonic acid, metabolized by cytochrome P450 and epoxygenases into EETs (epoxyeicosatrienoic acids), the final common activators of the TRPV4 pore. **(E)** Müller endfoot is a SER-rich compartment (MC), in contact with astrocytes (AsC) and the capillary endothelium (Endo). The yellow marker denotes the basement membrane; green denotes an astrocyte process that abuts the endfoot. **(F)** Calcium imaging in a dissociated mouse Müller cell. The cell responds to OAG (1-oleoyl-2-acetyl-sn-glycerol), a membrane-permeable analog of 1,2-diacylglycerol (DAG), a messenger activator of TRPC3/6/7 channels, with a large $[Ca^{2+}]_i$ increase. The bars in panels C and F denote the timing of drug application. From Ryskamp et al., 2014a); Molnar et al. (2016); P. Barabas, D.K. unpublished data (Created in Biorender.com).

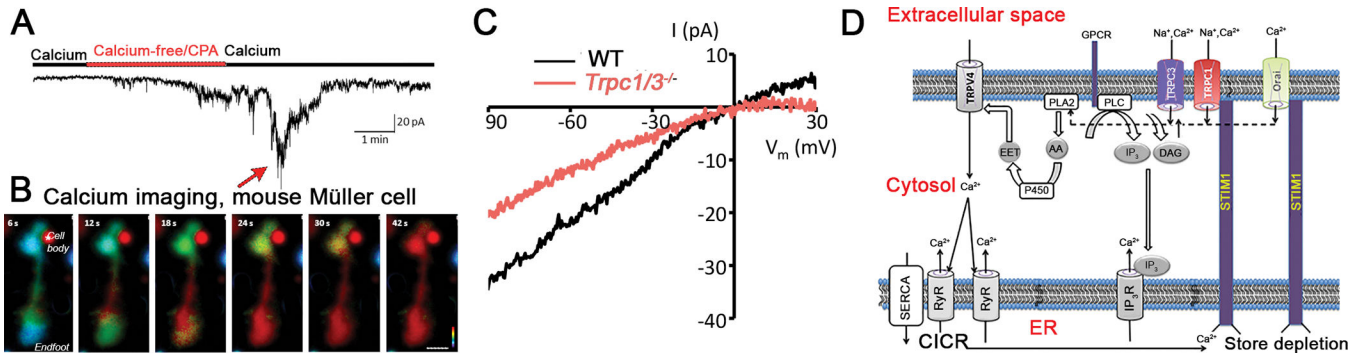

Fig. 3. Store operated Ca^{2+} entry (SOCE), Ca^{2+} induced Ca^{2+} release (CICR) and excitability in mouse Müller cells

(A) Mouse Müller glia, whole cell patch clamp recording. Depletion of the calcium endoplasmic reticulum (ER) store evokes a slowly developing inward current mediated by store-operated channels. Cyclopiazonic acid (CPA) inhibits calcium sequestration into the ER, resulting in its gradual emptying of stored Ca^{2+} in Ca^{2+}-free saline. The sensor proteins within the ER membrane ('STIM1' in panel D) communicate the depletion status to the plasma membrane to activate 'store-operated channels (TRPC1 and Orai in panel D). The slow inward current reflects Na^{+} influx through TRPC1. Restoration of 2 mM Ca^{2+} to the superfusing saline results in a transient activation of TRPC1 and Ca^{2+}-permeable Orai channels and large inward current that subsides when the ER compartment is reloaded with Ca^{2+}. **(B)** Calcium imaging, dissociated mouse Müller cell. The depletion-activated current marked with red arrow in panel A mediates $[Ca^{2+}]_i$ elevations mediated by TRPC1 and Orai channels and propagation of a Ca^{2+} wave from the endfoot towards the cell body that is presumably mediated by calcium store release channels (RyR and InsP3R in panel D). Scale bar, 5 μm. **(C)** The amplitude of the depletion-evoked inward current is reduced by targeted deletion of *Trpc1/3* genes. **(D)** Schematic model of store-operated signaling in Müller endfeet. Ca^{2+} -Induced Ca^{2+} release (CICR) is mediated by RyR and IP3R channels. In response to their activation by Ca^{2+} (RyRs) and IP3 (IP3Rs), Ca^{2+} is released from the ER lumen into the cytosol. Lowering of the lumenal $[Ca^{2+}]_{ER}$ triggers the depletion sensor, STIM1, which in turn activates TRPC1 and Orai channels within the plasma membrane and induces plasma membrane influx of cations, shown as inward current and calcium elevation in panels A–C. Store-operated and CICR mechanisms may interact with additional TRP subtypes such as TRPV4. TRPC3/6 channels are independently activated by diacylglycerol (DAG) downstream from phospholipase C (PLC) and G protein-coupled receptors (GPCRs). PLA2 (phospholipase A2), AA (arachidonic acid), EETs (epoxyeicosatrienoic acids), P450 (cytochrome P450) are obligatory proteins in the glial TRPV4 activation pathway.

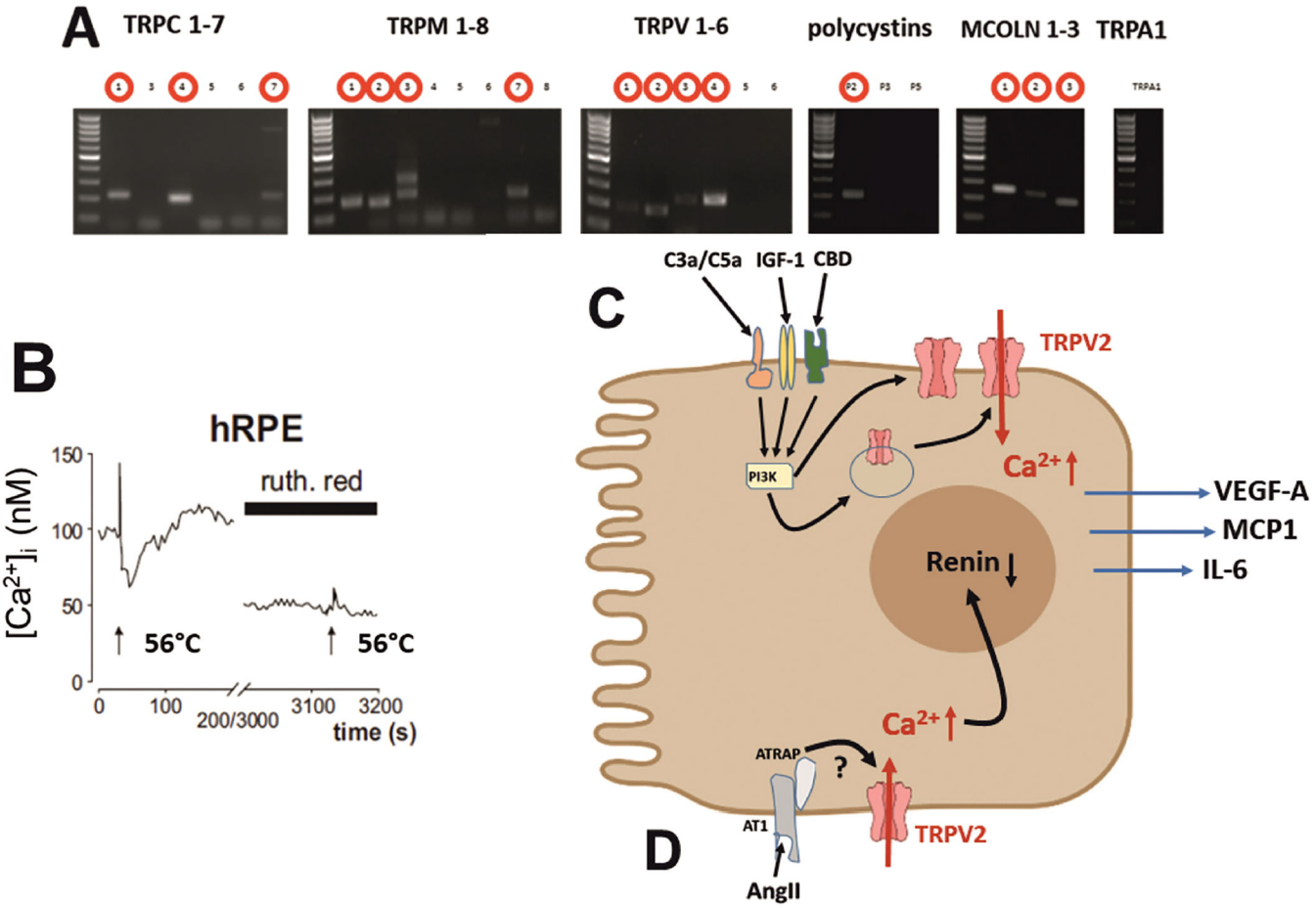

Fig. 4. TRPV2 activation modalities and differential regulation of the RPE.

(A) Spectrum of TRP channels expressed in freshly isolated human RPE cells analyzed by means of RT-PCR. **(B)** Heat-evoked Ca^{2+} transient in a human RPE cell is blocked by ruthenium red; indication for TRPV2 channel activation (Cordeiro et al., 2010). **(C)** Modalities of TRPV2 activation in the RPE by different G-protein coupled receptors by direct activation of the TRPV2 channel and/or by increase in surface expression of TPRV2 channel proteins mediated by PI3 kinase; activated TRPV2 channels promotes secretion of VEGF-A, MCP1 or IL-6 from the RPE. **(D)** AngII activated TRPV2 and the downregulation of renin expression in the RPE: AngII binds to AT1 receptors in the basolateral membrane of RPE and leads to an increase in $[Ca^{2+}]_i$ through activation of ATRAP under participation of an InsP3-sensitive intracellular Ca^{2+} store. The mechanism of ATRAP -dependent TRPV2 activation is unclear. $[Ca^{2+}]_i$ increase downregulates renin expression in the RPE via an unknown mechanism (Created in Biorender.com).

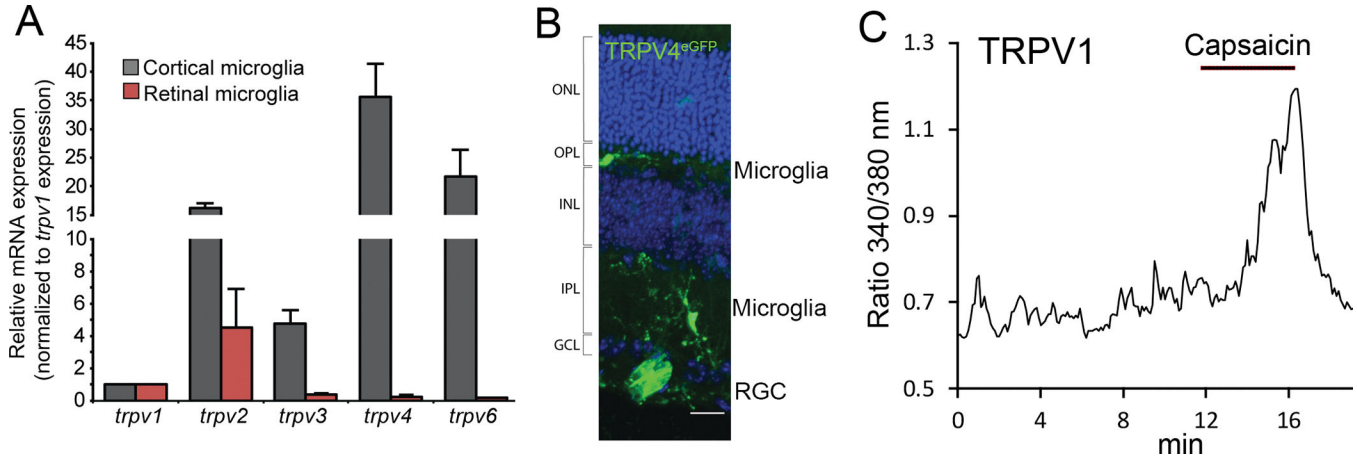

Fig. 5. TRP channel expression in retinal microglia.

(A) Expression of simultaneously measured vanilloid TRP transcripts in retinal (red bars) and cortical (gray bars) microglia shows overall transcript expression to be significantly lower in the retinal cohort. **(B)** TRPV4^{eGFP} retinas show lineage TRPV4 signals in RGCs and ramified IPL/OPL microglia. **(C)** TRPV1, calcium imaging. Dissociated retinal microglia respond to the agonist capsaicin with an increase in $[Ca^{2+}]_i$ (Redmon et al., 2021).

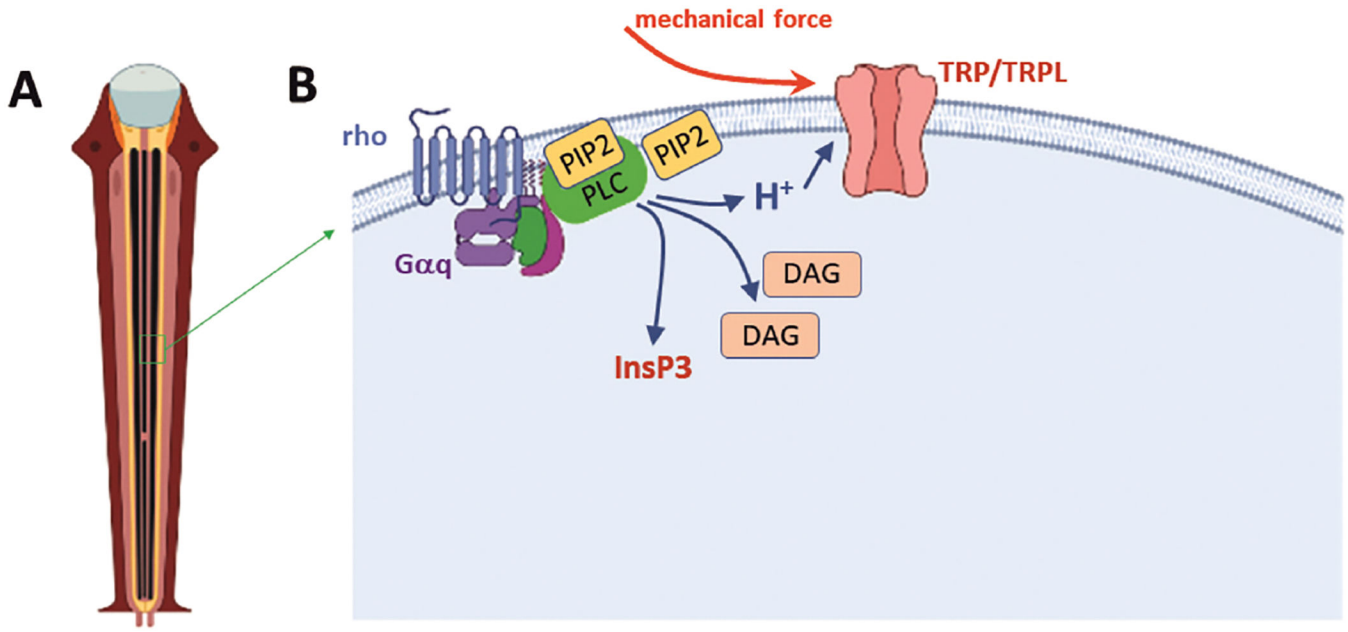

Fig. 6. Activation of TRP/TRPL channels in the rhabdomere of the Drosophila compound eye.
(A) Ommatidium of an insect eye represents a single eye of the compound eye; in dark brown the photosensitive cell, the rhabdomere. **(B)** Light-evoked signal transduction cascade in the microvilli membrane where all compounds of the cascade form a unit through binding with inaD. Light-dependent stimulation of rhodopsin leads to activation of PLC4β through Gαq type G protein. PLC cleaves InsP3 and DAG from the PIP2. This reaction leads to acidification and structural changes in the membrane in which phospholipids come closer and generate a mechanical force; the acidification and the mechanical force lead to activation of TRP/TRPL to generate the light-activated current (LIC) (Created in Biorender.com).

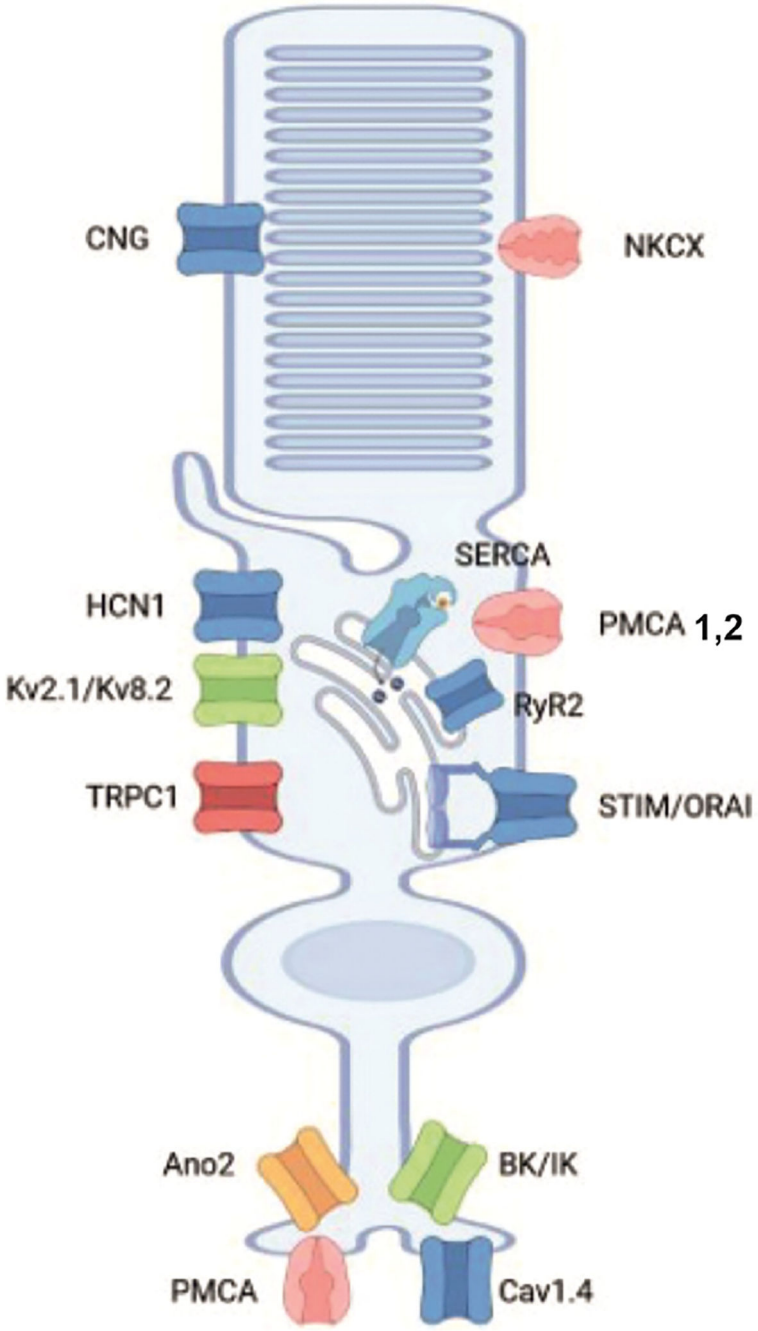

Fig. 7. Schematic presentation of a vertebrate photoreceptor.

Shown are those ion channels and transporters involved in signal processing and Ca^{2+} transport in photoreceptors. TRPC1 channels are shown as homomers in the photoreceptor cell body though it seems likely that they exist as heteromers of unknown composition. CNG: cyclic nucleotide-gated cation channel; NKCX: Na^{+},K^{+}-Ca^{2+} exchanger; HCN1: hyperpolarization-activated cyclic nucleotide-gated channel 1; SERCA: sarco-/endoplasmic reticulum Ca^{2+} ATPase; PMCA: plasma membrane Ca^{2+} ATPase: RyR2: ryanodine receptor

2; STIM: stromal interaction molecule; Ano2: anoctamine 2; BK/IK: Ca^{2+}-activated K^+ channels (Created in Biorender.com).

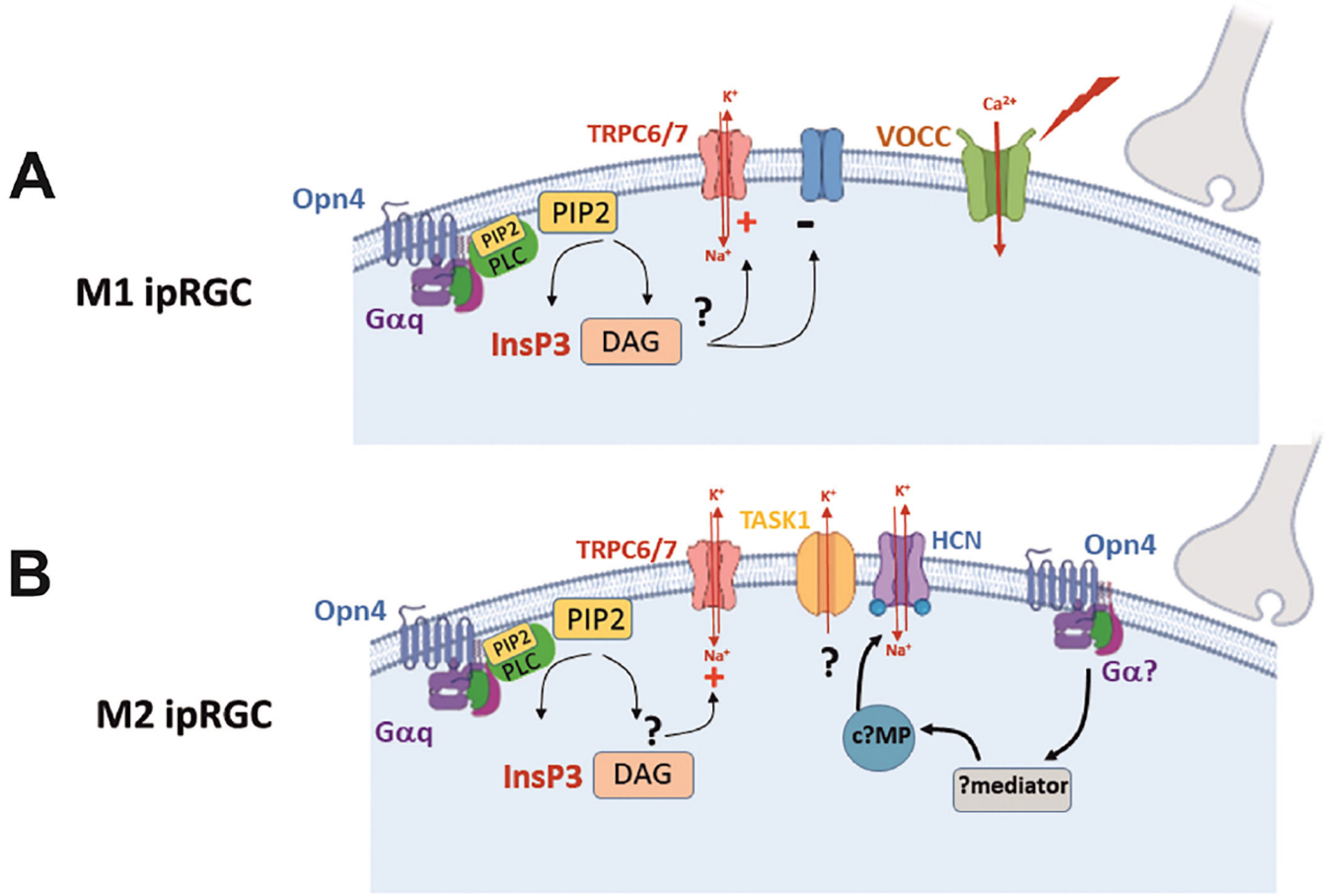

Fig. 8. TRP signal transduction in intrinsically photosensitive retinal ganglion cells (ipRGC).

(A) M1 ipRGC: Fast reacting M1 ipRGC's signal cascade starts with melanopsin (Opn4) that after perception of a photon activates Gαq/11 G protein that in turn leads to activation of PLCβ4 (PLC). PLCβ4 cleaves PIP2 into InsP3 and DAG, a reaction step that leads to activation of TRPC6/7 channels and/or inhibition of a background conductance K^+ channel (depending on the light intensity). As a result, the cell depolarizes and subsequenctly voltage-operated Ca^{2+} channels (VOCC) become active leading to increased action potential rates. The link betweem PLCβ4 activation and ion channel modulation is not clear. **(B)** M2 ipRGC: an ipRGC that reacts with slower amplitude and kinetics, using similar signaling cascade as the M1 ipRGC; participation of the K^+ channel (TASK1 or HCN) is not shown. M2 melanopsin activates an unknown Gα? to activate HCN channels and depolarize the cell. (Created in Biorender.dom).

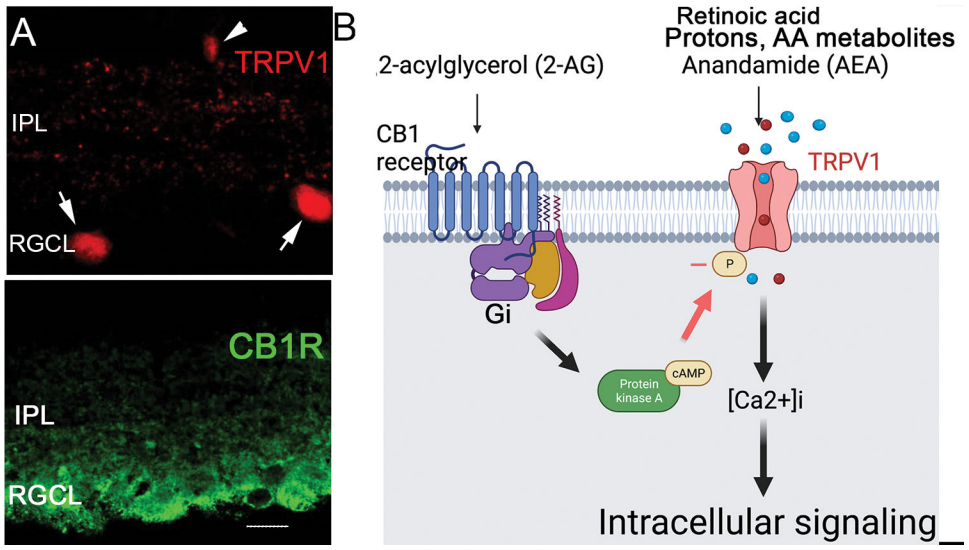

Fig. 9. TRPV1 signaling in RGCs.

(A) Confocal image from the retinal ganglion cell layer (RGCL) and inner plexiform layer (IPL) of transgenic adult $Trpv1^{Cre}$:Ai9 retina expressing the fluorescent marker tdTomato and immunolabelled with an antaibody raised against the Cannabinoid Receptor type 1 (CB1R). tdTomato signal shows sparse TRPV1 expression in RGC somata and processes (arrows), together with a presumed amacrine cell (arrowhead). Scale = 20 μm (Jo et al., 2017). **(B)** Hypothetical model of TRPV1 signaling in RGCs. The TRPV1 pore is activated by endocannabinoids (anandamide, AEA), protons and arachidonic acid metabolites such as 20-HETE and 12-HpETE. Another endocannabinoid, 2-acylglycerol, binds the CB1 receptor to initiate a Gi cascade that inhibits protein kinase A and suppresses cAMP-dependent facilitation of the TRPV1 channel. Endocannabinoid modulation of $[Ca^{2+}]_{RGC}$ therefore reflects the relative activation of the AEA vs 2-AG legs of RGC signal transduction.

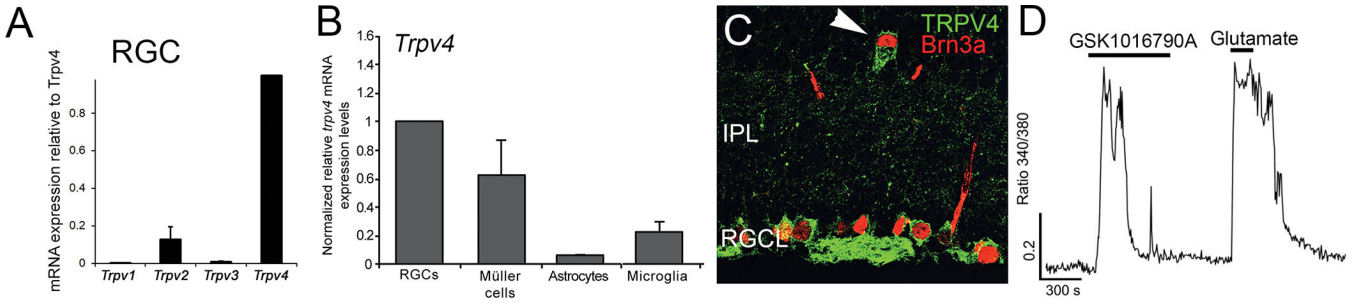

Fig. 10. Expression and function of vanilloid TRP channels in retinal ganglion cells.

(A) Relative expression of main vanilloid Trp genes in mouse RGCs. **(B)** Comparison of Trpv4 transcript abundance between RGCs, Müller glia, astrocytes and microglia shows prominent signal in RGCs. **(C)** Immunolabeling of mouse retinas for TRPV4 (green) and Brn3a (red) shows the channel is expressed in most RGCs, including the subpopulation of displaced cells in the proximal IPL. **(D)** TRPV4-mediated $[Ca^{2+}]_i$ signals in RGCs are large – comparable to responses obtained with saturating concentrations of glutamate.

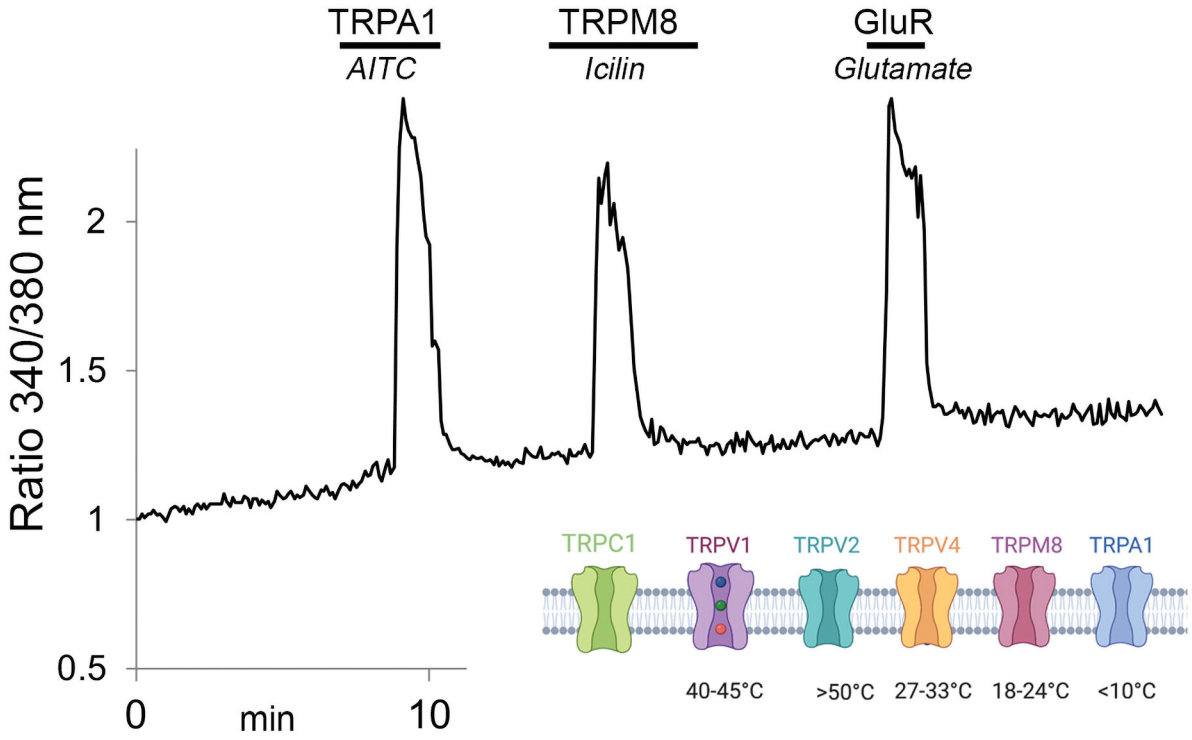

Fig. 11. RGCs functionally express thermoTRP channels.

Calcium imaging. Background-subtracted 340/380 ratio of calcium signals in Fura-2 indicator-loaded mouse RGCs. The TRPA1 channel agonist allyl isothiocyanate (AITC) and TRPM8 agonist icillin induce $[Ca^{2+}]_i$ elevations comparable in size to the signal induced by glutamate. Data acquired by A. Jo. Inset: Schematic of temperature optima of thermoTRP channels known to be expressed in mammalian RGCs (Created in Biorender.com).

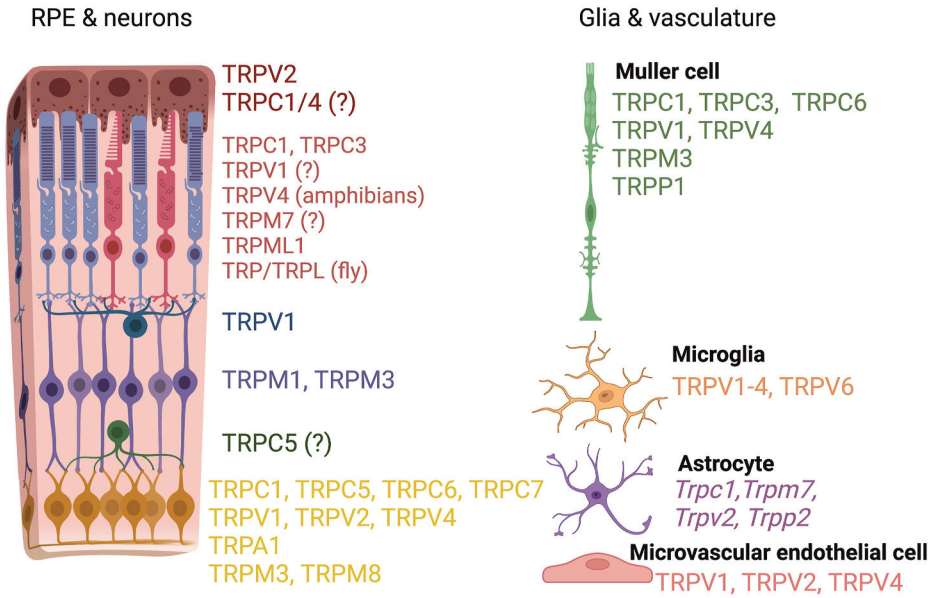

Fig. 12. Summarizing overview of the TRP channel expression in the different cell types of the retina.

TRP family members written in capitals refer to evidence for protein expression and/or functional evidence; those in italics refer to gene expression data only; question marks indicate involvement of TRP channel subtypes with open questions. (created in Biorender.com).