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TRPM1: The endpoint of the mGluR6 signal transduction cascade in retinal ON-bipolar cells

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Abstract

For almost 30 years the ion channel that initiates the ON visual pathway in vertebrate vision has remained elusive. Recent findings now indicate that the pathway, which begins with unbinding of glutamate from the metabotropic glutamate receptor 6 (mGluR6), ends with the opening of the transient receptor potential (TRP)M1 cation channel. As a component of the mGluR6 signal transduction pathway, mutations in TRPM1 would be expected to cause congenital stationary night blindness (CSNB), and several such mutations have already been identified in CSNB families. Furthermore, expression of TRPM1 in both the retina and skin raises the possibility that a genetic link exists between certain types of visual and skin disorders.

Keywords

bipolar cell; metabotropic glutamate receptor; retina; synaptic transmission; TRP channel

Introduction

One of the earliest steps in visual processing is the generation of parallel information channels responding to increases *versus* decreases in light intensity [1]. These ON and OFF responses originate at the first retinal synapse where two classes of postsynaptic bipolar cells respond with opposite polarities to glutamate, the neurotransmitter released by photoreceptors (see Fig. 1). Rod and cone photoreceptors are depolarized in the dark, which results in the tonic release of glutamate into the synaptic cleft [2]. Light causes photoreceptors to hyperpolarize, thereby reducing the rate of glutamate release [3]. The light-induced decrease in the synaptic glutamate concentration causes hyperpolarization of OFF-bipolar cells and depolarization of ON-bipolar cells. The opposite responses of ON- and OFF-bipolar cells arise from their expression of distinct classes of glutamate receptors [4]. The dendrites of OFF-bipolar cells contain ionotropic glutamate receptors of the AMPA/kainate class, which are glutamate-gated cation channels. In contrast, ON-bipolar cell

dendrites express a unique metabotropic glutamate receptor 6 (mGluR6) [5]. The OFF-bipolar cell response is relatively straightforward – glutamate directly activates a depolarizing cation current in the dark, which is deactivated in response to the light-induced decrease in synaptic glutamate. In contrast, the depolarizing response of ON-bipolar cells is more complex, involving a signal transduction pathway that has been the focus of intense investigation for over 20 years.

In ON-bipolar cells, the light-induced deactivation of the mGluR6 signal transduction pathway culminates in the opening of a non-selective cation channel. Until recently, mGluR6 and the G protein Go [6, 7] were the only components of the pathway that had been identified at the molecular level. The mGluR6 pathway bears analogy to phototransduction, where activation of rhodopsin by light activates the G protein, transducin, leading to the closure of cyclic guanosine monophosphate (cGMP)-gated channels and hyperpolarization of the photoreceptor [8]. Based on this analogy and the similarities in the currents, retinal neuroscientists pursued the idea that the mGluR6-coupled channel would also be a cGMP-gated channel [9, 10]. It is now known that cGMP does not gate the ON-bipolar cell channel directly, though it exerts a strong modulatory effect [11].

More recently, the emergence of transient receptor potential (TRP) channels and their wide-ranging roles in sensory transduction has led retinal neuroscientists increasingly to place their bets on a member of the TRP channel family being the mGluR6-coupled channel in ON-bipolar cells. Shen *et al.* [12] showed that the mGluR6-coupled current in ON-bipolar cells is inhibited by TRP channel antagonists such as ruthenium red and capsazepine. Furthermore, Shen *et al.* [12] demonstrated that capsaicin and anandamide, both considered selective agonists of TRPV1, evoked a similar current; however, the transduction current and response to these agonists were unaltered by genetic ablation of TRPV1. Now, nearly 30 years after the ON-bipolar cell transduction current was first discovered [13], mGluR6 has been demonstrated to be coupled to TRPM1 [14, 15].

Initial clues that TRPM1 is required for ON-bipolar cell signaling

Initial clues that TRPM1 is required for ON-bipolar cell signaling were provided by *in situ* hybridization studies showing selective expression of TRPM1 mRNA in retinal bipolar cells [16, 17]. The real breakthrough, however, came in 2008 in a report linking the TRPM1 gene to congenital night blindness in Appaloosa horses [18]. Known for their spotted coats, Appaloosa horses express two versions of the pigmentation gene, LP and lp, giving rise to the variations in Appaloosa coloring. Significantly, horses that are homozygous LP/LP tend to have a largely white coat with few spots and are also night blind. Electroretinograms (ERGs) on these horses indicate defective signal transmission between the photoreceptors and retinal ON-bipolar cells (*i.e.*, selective loss of the b-wave) [18]. Bellone *et al.* mapped *TRPM1* to the LP locus and showed that *TRPM1* expression was dramatically reduced in the LP/LP animals, namely to 0.05% of normal. It should be noted that in their article, Bellone *et al.* referred to a 2007 abstract by Koike *et al.* [16], describing abnormal electrophysiologic activity in the retina of a TRPM1-knockout mouse. Since then, several other groups have confirmed TRPM1 expression in ON-bipolar cells and reported a similar “no b-wave” ERG phenotype in TRPM1-knockout mice [12, 14, 15].

TRPM1: The endpoint of the mGluR6 signal transduction pathway

To seal the case that TRPM1 is the endpoint of the mGluR6 pathway, two groups demonstrated that TRPM1 is localized to ON-bipolar cell dendrites (as shown in Fig. 2) and that the mGluR6-coupled current is absent in the TRPM1^{-/-} retina. Morgans *et al.* [14] used a TRPM1^{-/-} mouse produced by Lexicon Genetics and tested the effect of the knockout on the mGluR6-coupled current by patch-clamp recordings of bipolar cells in retinal slices. In these experiments, Morgans *et al.* [14] bypassed photoreceptors entirely by using pharmacology to create virtual light responses. Retinal slices were bathed in the mGluR6 agonist L-AP4 to simulate darkness; pressure application of the mGluR6 antagonist cyclopropyl-4-phosphonophenylglycine (CPPG) to the ON-bipolar cell dendrites was then used to simulate a light flash.

Responses to CPPG from rod bipolar cells (which in mammals are all ON-type) were abolished in the TRPM1^{-/-} retina, as were the responses from many of the cone ON-bipolar cells (approximately 50% of cone bipolar cells are ON-type and 50% OFF-type). Interestingly, some cone ON-bipolar cells retained a small, transient CPPG-triggered current, suggesting that a second mGluR6-coupled channel is present in these cells. Sustained and transient ON bipolar cell responses have been described in salamander by Awatramani and Slaughter [19], who suggested that this dichotomy originates most probably in the mGluR6 transduction pathway. Further, Morgans *et al.* [14] showed that the capsaicin-sensitive current described by Shen *et al.* [12] persisted in some bipolar cells in the TRPM1^{-/-} mice, though it tended to be less common and smaller in amplitude. Again, this suggests that another channel, in addition to TRPM1, may be involved in generating the wild-type ON-bipolar cell light response.

Koike *et al.* [15] created their own TRPM1^{-/-} mice by targeted gene disruption and measured light responses from ON-bipolar cells using perforated-patch whole-cell clamp. They found that ON-bipolar cells in TRPM1^{-/-} retinal slices were unresponsive to light, whereas the OFF-bipolar cells were unaffected (an important control indicating normal transmission from the photoreceptors). Both groups compared optokinetic responses of wild-type and TRPM1^{-/-} mice and found a reduction in both contrast sensitivity and spatial frequency threshold, indicating that TRPM1^{-/-} mice are visually impaired but not blind [14, 15], similar to other mutations that selectively block the ON pathway [20].

Koike *et al.* then went a step further and reconstituted the mGluR6-based signaling pathway in a heterologous system in a direct demonstration of mGluR6-dependent regulation of TRPM1 activity. They showed that the TRPM1 current could be suppressed by application of glutamate in cells co-transfected with mGluR6 and Gαo, or when TRPM1 was co-transfected with a constitutively active form of Gαo [15]. A key finding was that the pathway was intact in outside-out and inside-out patches of plasma membrane pulled from the transfected cells [15]. This suggests that the mGluR6 signal transduction pathway is membrane-delimited and does not require soluble, cytoplasmic factors. Furthermore, Koike *et al.* reported that application of activated Gαo to the cytoplasmic face of excised patches resulted in deactivation of the TRPM1 current. In contrast, two recent abstracts report that it

is actually the G protein $\beta\gamma$ subunits that close TRPM1 and turn off the constitutively active TRPM1 current [21, 22].

TRP channels

Transient receptor potential channels were first discovered 40 years ago through characterization of a spontaneous mutation in *Drosophila*, which renders the flies blind under bright illumination [23]. In 1989, Montell and Rubin [24] identified the mutation and cloned the founding member of this ion channel family. The so-called *Drosophila* TRP channel is a calcium-permeable cation channel found in a protein complex in the photoreceptor rhabdomeres. In 1992, a second TRP-like channel, TRPL, was cloned from *Drosophila* photoreceptors [25]. TRPL subunits form a non-selective cation channel that is strongly inhibited by intracellular calcium. Together, TRP and TRPL generate sustained and transient components of the light response in *Drosophila* photoreceptors. This brings to mind the sustained, TRPM1-dependent component and the transient component of unknown origin identified in the CPPG response of cone ON-bipolar cells in the mouse retina [14], raising the possibility of an evolutionary relationship between these two pathways.

Over the past decade, an abundance of mammalian TRP homologs have been discovered and implicated in sensory functions, ranging from nociception to thermosensation (reviewed recently by Venkatachalam and Montell [26]). TRP channels share a common structure, with six predicted transmembrane domains and a re-entrant P-loop, which is proposed to form the pore of the channel, as it does in voltage-gated ion channels. In addition, a highly conserved 23–25 amino acid TRP domain is located in the cytoplasmic region, close to the sixth transmembrane domain. TRP channels can be subdivided into several subfamilies. The canonical TRPC channels are primarily activated by phospholipase C-dependent mechanisms, although some may be activated by depletion of intracellular Ca^{2+} stores as well. The TRPV channels, whose members can be activated by heat [27], osmotic cell swelling [28], and low intracellular Ca^{2+} , play a role in nociception and Ca^{2+} reabsorption in the kidneys [29]. Members of the TRPM channel family have been shown to function in insulin secretion (TRPM3) [30], taste transduction (TRPM5) [31], and thermosensation (TRPM8) [32]. Two other members of this family, TRPM6 and TRPM7, are thought to be involved in magnesium homeostasis [33], and TRPM2 forms a non-selective cation channel gated by ADP-ribose and intracellular Ca^{2+} [34].

TRPM1: The first discovered, but least known of the TRPM subfamily

TRPM1 is the founding member of the TRPM subfamily of TRP channels, and was initially identified by differential display as a potential suppressor of tumor metastasis (and named melastatin because it is down-regulated in metastatic melanoma) [35]. TRPM1 is the product of a complex gene, spanning 58 kb and 27 exons, and is subject to extensive alternate mRNA splicing to yield several long isoforms predicted to form ion channels as well as multiple short isoforms encoding polypeptides that overlap with either the N- or C-terminal cytoplasmic domains of full-length TRPM1 [15, 36–39]. Despite being the first of the TRPM gene family discovered, TRPM1 has remained the most enigmatic of the TRPM channels with regard to its cellular function and biophysical properties. Evidence that

TRPM1 is, in fact, an ion channel has been hard to come by. Until 2009, the only demonstration of TRPM1 activity was provided by Xu *et al.* [37], who used fluorescence imaging techniques to show that calcium was elevated in human embryonic kidney 293 (HEK293) cells transiently expressing TRPM1. In these experiments, Xu *et al.* [37] made the intriguing observation that calcium levels were lower when the full-length ion channel was co-transfected with one of the short N-terminal isoforms, suggesting a physical interaction between the two isoforms that suppressed channel activity.

Despite the functional imaging results, no one had reported recordings of TRPM1-mediated currents until 2009 when Oancea *et al.* [38] reported endogenous outwardly rectifying non-selective cation currents in B16-F10 epidermal melanocytes that could be reduced by microRNA knock-down of TRPM1 expression. They showed that a similar current was generated by expression of TRPM1 in human melanoma cells. Shortly thereafter, Koike *et al.* [15] reported constitutively active inward currents in CHO cells transfected with TRPM1. There are some puzzling differences, however, in the biophysical properties of the TRPM1 currents reported by these groups. For example, the current-voltage relation of the ON-bipolar cell transduction channel displays a moderate outward rectification [12], and that reported by Oancea *et al.* [38] exhibits very strong outward rectification; in contrast, the TRPM1 current reported by Koike *et al.* [15] is linear. These discrepancies may reflect differences in the ionic composition of the recording solutions, or, more interestingly, they may reflect expression of additional channel subunits or TRPM1 splice variants.

TRPM1: A new locus for congenital stationary night blindness

As a component of the transduction pathway in ON-bipolar cells, TRPM1 is a prime candidate for mutations causing congenital stationary night blindness (CSNB). Two forms of CSNB, termed complete (CSNB1) and incomplete (CSNB2), have been characterized in humans and animal models [40]. The diagnostic signature of both is a “negative” ERG in which the a-wave, arising from photoreceptor transduction, is normal, but the b-wave, arising from ON-bipolar cell activation, is either absent (CSNB1) or reduced (CSNB2). At the molecular level, CSNB1 mutations block ON-bipolar responses without affecting glutamate release from photoreceptors, or OFF-bipolar cell responses, while CSNB2 mutations impair the control of glutamate release from photoreceptors, thus affecting both ON- and OFF-bipolar cell responses. So far, all known causes of CSNB2 are mutations in pre-synaptic proteins unique to photoreceptors [(CACNA1F, the photoreceptor calcium channel, and calcium-binding protein 4 (CBP4)]; in contrast, all known mutations causing CSNB1 occur in components of the post-synaptic mGluR6 signal transduction pathway (mGluR6, nyctalopin, and now TRPM1). The small b-wave seen in the CSNB2 ERG is presumably due to residual release of glutamate from cone photoreceptors accounted for, in the case of CACNA1F mutations, by additional calcium channel types present in cone photoreceptors [41].

Four recent articles now report an association between mutations in the TRPM1 gene and autosomal recessive CSNB1 in human patients [42–45]. In aggregate, a total of 37 distinct mutations were observed in 21 patients. One mutation was a deletion of eight exons from the TRPM1 locus. Three mutations were small (single-base) deletions that produced a shift in

the TRPM1 reading frame, resulting in a string of altered amino acids and premature termination of the TRPM1 protein. Another six mutations introduced a non-sense codon and are expected to encode a truncated protein. A further nine TRPM1 alleles show base differences in the proximity of mRNA splice sites, suggesting that they cause an alteration of TRPM1 isoform expression.

More interesting from the point of view of understanding TRPM1 function are 18 missense mutations that are predicted to encode amino acid substitutions. Five missense mutations result in amino acid substitutions in or close to the transmembrane region. One possibility is that these mutations result in a non-conducting TRPM1 channel. Alternatively, the channel may be constitutively open, possibly resulting in a degeneration of ON-bipolar cells. A further five missense changes are located very close to the N terminus of the protein (in the first 139 amino acids of h109 + TRPM1), and another five mutations encode amino acid changes in the N-terminal intracellular region (between Leu364 and Pro611). Most likely these regions are important for proper trafficking of TRPM1 to ON-bipolar cell dendrites, or for its interaction with intracellular signaling molecules. Nakamura *et al.* [45] investigated the effects of two missense mutations (one within the N-terminal cytoplasmic domain and the other at the end of the transmembrane domain) on TRPM1 trafficking using electroporation of newborn mice to introduce plasmids encoding wild-type or mutant TRPM1 under the control of the mGluR6 promoter. For both mutants, transfected ON-bipolar cells showed a reduced expression in the dendrites relative to the cell body compared to wild-type, suggestive of a trafficking defect. Finally, one mutation (R1438G) was found in the C-terminal intracellular domain [42]. Because it was found in cis with another mutation in the transmembrane region; however, it is not known if the C-terminal domain mutation is deleterious.

While mutations in TRPM1 appear to account for about half the cases of CSNB1, and mutations in NYX (nyctalopin) and GRM6 (mGluR6) explain another 25–40% of the cases, the remainder CSNB1 patients do not appear to carry mutations in these three genes, suggesting that additional genes may contribute to CSNB1.

Is TRPM1 the bipolar cell antigen in melanoma-associated retinopathy?

TRPM1 expression occurs predominantly in the eye and skin [15]; thus it is logical to ask whether the visual deficits caused by TRPM1 mutations are accompanied by skin abnormalities. Long and short isoforms have been detected in both retina and skin [15, 36–39]. In metastatic melanoma, the mRNA splicing equilibrium appears to shift towards the shorter isoforms [36].

Oancea *et al.* [38] demonstrated that knock-down of TRPM1 in epidermal melanocytes led to a reduction in melanin pigment, leading them to speculate that TRPM1 may have a role in pigmentation. Certainly, in the Appaloosa horse, there is a clear association between coat pattern and CSNB [46], but no abnormal pigmentation was reported in the TRPM1^{-/-} mice [14, 15]. In humans, Li *et al.* [42] reported that their CSNB patients with TRPM1 mutations appear to have normal pigmentation, but all probands experienced other skin conditions, such as dry or scaly skin.

A rare condition possibly tying TRPM1 to diseases of both the skin and the eye is melanoma-associated retinopathy (MAR). Metastatic cutaneous melanoma is associated with a down-regulation of TRPM1 (previously known as melastatin 1), with MAR occurring in a subset of patients. The visual deficits in MAR include night blindness and a progressive loss of vision. ERG recordings from these patients show a classic “negative” waveform similar to that observed in CSNB, and serum from these patients contains antibodies that label retinal bipolar cells. Thus MAR is believed to be caused by an autoimmune response to retinal antigens expressed by the tumor [47, 48]. In view of the shared expression of TRPM1 by melanocytes and retinal bipolar cells, TRPM1 seems a likely candidate for the MAR antigen.

Conclusion

A confluence of evidence from many labs has ended a decades-long quest in identifying TRPM1 as the mGluR6-coupled cation channel in retinal ON-bipolar cells, the first physiologic role demonstrated for TRPM1. Within the retina, TRPM1 is expressed by retinal ON-bipolar cells, where it is localized to the cell bodies and dendrites [14, 15]. It appears to be a constitutively active cation channel that is closed in the dark by glutamate binding to mGluR6 and activation of G α o [15]. It is likely, though, that TRPM1 is not the only mGluR6-coupled channel. Evidence for an additional channel is provided by the residual transient mGluR6-coupled currents in some cone ON-bipolar cells in the TRPM1^{-/-} retina, as well as capsaicin-sensitive currents that persist in TRPM1^{-/-} ON-bipolar cells [14]. Similar to genes encoding other components of the mGluR6 signal transduction pathway, mutations in the TRPM1 gene have been associated with complete CSNB [42–45]. In addition to retinal ON-bipolar cells, TRPM1 is also expressed by melanocytes in the skin [35], and may be linked to diseases affecting both cell types, such as MAR.

Despite the surge of recent discoveries about TRPM1, tantalizing unknowns remain. First, is TRPM1 the sole component of the mGluR6-coupled ion channel in rod bipolar cells? Differences between the ON-bipolar cell transduction current and currents from heterologously expressed TRPM1 could be explained by differences in channel composition. Second, are other transduction channels present in a subset of ON-bipolar cells as suggested by the transient CPPG-triggered currents and capsaicin responses in the TRPM1^{-/-} retina? Finally, and most importantly, what is/are the second messenger/s that directly bind to TRPM1 and regulate channel activity?

Abbreviations

mGluR6	metabotropic glutamate receptor 6
CSNB	congenital stationary night blindness
AMPA	α -amino-3-hydroxyl-5-methyl-4-isoxazole-propionate
cGMP	cyclic guanosine monophosphate
TRP	transient receptor potential

TRPL	transient receptor potential-like
ERG	electroretinogram
CPPG	cyclopropyl-4-phosphonophenylglycine
MAR	melanoma-associated retinopathy

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Figure 1.

Schematic representation of the layers and cell classes in a mammalian retina (left). Rod and cone photoreceptors (top) transduce light signals into a regulated release of glutamate at ribbon synapses (top right box). All photoreceptors respond to light by hyperpolarization, as do horizontal cells (HC) and OFF bipolar cells (pink), which express AMPA and kainate-type glutamate receptors (GluA and GluK). ON-bipolar cells depolarize in response to light, a mechanism involving mGluR6 and TRPM1 channels. The G protein signaling cascade activated by mGluR6 is represented at the bottom right. The function of nyctalopin (NYX) and the second messenger signal between Go and the TRPM1 channel remain unknown.

Figure 2. Confocal microscopic image of a vertical section of macaque retina showing TRPM1 immunofluorescence (green) and rod bipolar cells labeled with an antibody against PKC α (red) superimposed over a Nomarski image of the section (blue). Abbreviations: opl, outer plexiform layer; inl, inner nuclear layer; ipl, inner plexiform layer; gcl, ganglion cell layer. The scale bar represents 10 μ m.