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Review

TRPM1: A vertebrate TRP channel responsible for retinal ON bipolar function

Chieko Koike[a,c,d], Tomohiro Numata[e], Hiroshi Ueda[f], Yasuo Mori[e], Takahisa Furukawa[a,b,*]

[a] Department of Developmental Biology, Osaka Bioscience Institute, 6-2-4 Furuedai, Suita, Osaka, 565-0874, Japan
[b] JST, CREST, Osaka Bioscience Institute, 6-2-4 Furuedai, Suita, Osaka, 565-0874, Japan
[c] College of Pharmaceutical Sciences, Ritsumeikan University, 1-1-1 Noji-Higashi, Kusatsu, Shiga, 525-8577, Japan
[d] PRESTO, JST, 4-1-8 Honcho, Kawaguchi, Saitama 332-0012, Japan
[e] Department of Synthetic Chemistry and Biological Chemistry, Graduate School of Engineering, Kyoto University, Katsura Campus, Nishikyo-ku, Kyoto, 615-8510, Japan
[f] Department of Biomolecular Science, Faculty of Engineering, Gifu University, 1-1 Yanagido, Gifu, 501-1193, Japan

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ABSTRACT

The transient receptor potential (TRP) channels affect essential functions widely in sensory systems of various species, both invertebrates and vertebrates. The channel protein encoded by the *trp* gene, the first identified TRP superfamily molecule, is known to mediate the *Drosophila* light response. A vertebrate TRP channel playing a crucial role in the visual system has not yet been discovered, although numerous studies have revealed primal functions of TRP superfamily molecules in various sensory systems other than vision. In the retina, which is the entry tissue in the vertebrate visual pathway, the transduction cation channel in ON bipolar cells has been elusive, despite intensive investigation by many researchers over a long period of time. Recent studies finally revealed that TRPM1, the first member of the melanoma-related transient receptor potential (TRPM) subfamily to be discovered, is a visual transduction channel in retinal ON bipolar cells. This review covers the significant discoveries on the physiological function and regulatory mechanism of the TRPM1 channel in retinal ON bipolar cells and the association of human TRPM1 mutations with congenital stationary night blindness.

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1. Introduction

1.1. TRP channels

TRP channels crucially and broadly serve in sensory reception in various living organisms [1,2]. Numerous studies have shown that TRP channels are involved in vision, taste, olfaction, hearing and touch, in addition to thermo- and osmosensation. Their functional roles are important not only in classical sensory transduction in various species but also in infrared detection by snakes [3]. Among the traditional five mammalian senses, originally classified by Aristotle, only vision seemed not to essentially require any TRP channel activity. A TRP channel was first reported in *Drosophila*, showing its essential role in the photoreceptor response to light [1,4]. Therefore, the presence of TRP channels in vertebrate visual function has been predicted for decades. However, a TRP channel playing a crucial role in vertebrate vision was not identified until recently.

1.2. ON and OFF pathway in visual processing

In the vertebrate visual system, the retina is the only part of the central nervous system that mediates photoreception. Visual processing begins with the conversion of photons to neural signals in the retinal photoreceptors, except for certain non-image-forming responses that rely on intrinsic photosensitive retinal ganglion cells (ipRGC) containing melanopsin. The two types of photoreceptors, rods and cones, are distinguished by shape, type of photopigment they contain, distribution across the retina, and pattern of synaptic connections. High-acuity color vision is mediated by cone photoreceptors, while the response to dim light is mediated by rod photoreceptors. Photoreceptors make synapses with two types of interneurons, horizontal cells and bipolar cells. Photoreceptors relay neural signals to a number of bipolar cells. Bipolar cells in turn convey these signals to the ganglion cells, and then finally retinal ganglion cells, the digital output neurons of the retina, transmit the result of all of the information processing to the brain through the optic nerve. Horizontal cells and amacrine cells modify this central signal transmission.

A fundamental feature of the vertebrate visual system relies on the functional separation of neuronal signaling into the ON and OFF pathways that generate visual contrast. These two pathways originate in depolarizing ON bipolar cells and hyperpolarizing OFF bipolar cells, which receive signals from photoreceptors that reduce

* Corresponding author at: Department of Developmental Biology, Osaka Bioscience Institute, 6-2-4 Furuedai, Suita, Osaka, 565-0874, Japan. Tel.: +81 6872 4853; fax: +81 6872 3933.
E-mail address: furukawa@obi.or.jp (T. Furukawa).

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the glutamate release by light-evoked hyperpolarization [5,6]. In mammal retinas, rod and cone photoreceptors form synapses with rod and cone bipolar cells, respectively. All rod bipolar cells are the ON type, and cone bipolar cells are subdivided into ON and OFF types. The functional diversity of bipolar cells is the result of the expression of different glutamate receptors (GluRs) at the postsynaptic region [7]. ON bipolar cells express a metabotropic GluR, mGluR6, on dendrites that make invaginating contacts with photoreceptor terminals, while OFF bipolar cells express ionotropic GluRs (AMPA/Kainate receptors), glutamate-gated cation channels, on dendrites making flat contacts with photoreceptor terminals [8–10]. In the dark, glutamate released from photoreceptors depolarizes OFF bipolar cells through activation of an ionotropic glutamate receptor, whereas glutamate hyperpolarizes ON bipolar cells through activation of mGluR6 with a decrease in cationic conductance [11–13]. Unlike ionotoropic GluRs, which function as channels themselves, mGluR6 in ON bipolar cells requires the cation channel to mediate visual transduction. This transduction cation channel in ON bipolars had been a missing piece in visual processing despite intensive investigation.

1.3. Predicted visual transmission channel in retinal ON bipolar cells

The visual transduction channel in retinal ON bipolar cells had been described as a cGMP-gated channel in multiple physiology textbooks without conclusive evidence. The cGMP-gated cation channel in ON bipolar cells had been hypothesized to be closed by increasing the rate of cGMP hydrolysis through phosphodiesterases (PDEs) by a G-protein-mediated process that is strikingly similar to light transduction in photoreceptors [14]. In ON bipolar cells, the mGluR6 receptor couples to a heterotrimeric G-protein complex, Go [15,16]. Signals require Goα, which ultimately closes a downstream non-selective cation channel in ON bipolar cells [15,17–19]. It appears that Goα is required in the closure of the cation channel, but there is no evidence that PDE is involved in the regulation in terms of function and distribution [17]. At present, cGMP is considered to play a modulatory role in visual transmission if it is involved at all [20].

2. TRP families in the retina

The TRP channel was first cloned in *Drosophila* to examine its essential role in the photoreceptor response to light [1,4]. However, there are distinctive differences in retinal structure and phototransduction mechanisms between *Drosophila* and vertebrate eyes. Light stimulus depolarizes rhabdomeric-type photoreceptors through Gq-coupled photopigments in *Drosophila*, but hyperpolarize ciliary-type photoreceptors through Gt-coupled photopigments in vertebrate photoreceptors. Mechanisms of light perception in vertebrate photoreceptors involve photopigments, PDE and cGMP-gated channels, but do not seem to involve TRPs. In fact, interestingly, neither rods nor cones but light-sensitive ipRGCs, coupled with pupil constriction and circadian rhythms, gave initial clues to a possible role for TRP in vertebrate photoreception. Mouse TRPC3, a homolog of *Drosophila* Trp and Trpl, is activated downstream of melanopsin in a reconstitution system using cultured cells, and utilizes Gq family G protein, as does *Drosophila* phototransduction. However, it should be noted that immunohistological analysis showed that ipRGCs express only TRPC6 and TRPC7 [21], not TRPC3 or TRPC1. Thus the exact roles of particular TRP channels in ipRGCs, especially prime candidates TRPC6 and TRPC7, still require future analysis. In contrast, almost nothing had been known regarding a significant role of TRPs in the vision-forming classical light perception pathway.

2.1. The isolation of TRPM1

TRPM1, also known as *melastatin*, was the first member of the TRPM subfamily cloned [22,23]. In 1998, Duncan et al. [22] identified a 2722 bp length mouse *melastatin* cDNA, later named *TRPM1-S*, in a differential display approach between poorly and highly metastatic B16 melanoma cell lines. The expression pattern of *melastatin* was reversely correlated with metastatic potential in mouse and human cell lines, and melanocytic neoplasm, and correlated with pigmentation in melanoma cell lines [22,24]. A recent study reported that human TRPM1 is regulated by p53 which can be induced by ultraviolet light [25]. However, the exact physiological role of TRPM1 *in vivo* remained unknown. Duncan et al. also detected the expression of *melastatin* in the mouse eye by RT-PCR, and cloned a full-length human *Melastatin* cDNA from a human retinal library. They investigated the possibility that *Melastatin* mutation was responsible for the *ruby-eye-2* mutation, which causes a light color coat and red eye, however, this possibility was refuted [22,26].

In order to identify genes that are potentially important for retinal development and/or function we screened EST clones highly enriched in the mouse retina [27]. We identified a mouse *TRPM1-L* cDNA corresponding to the human *TRPM1* long form (GenBank Accession Number #AY180104) and found by *in situ* hybridization that the TRPM1 transcript is specifically expressed in the inner nuclear layer of the mouse retina [28]. The mouse *TRPM1-L* encodes a predicted 1,622 amino acid protein, containing six transmembrane domains, an ion transporter domain and a TRP domain, as do other TRP family members, whereas TRPM1-S is an N-terminal truncated form lacking the six transmembrane domains and the other domains as well.

2.2. The differential expression of TRPM1-S and -L in the mouse retina

We examined the expression difference between *TRPM1-S* and–*L* on the mouse retina. Mouse *TRPM1-L* and *-S* transcripts were both detected in the retina, whereas only the *TRPM1-S* transcript was detected in the skin [28,29]. Intriguingly, the expression pattern of *TRPM1-L* and–*S* transcripts were different in the retina. *TRPM1-L* transcripts were observed at postnatal stages in the inner nuclear layer corresponding to the localization of Chx10, a pan-bipolar marker [28]. A faint *TRPM1-S* signal was also detected in the inner nuclear layer. The expression of TRPM1-S was reported in the retinal pigment epithelial (RPE) during embryonic stages, however, TRPM1-L was not detected in the RPE [28].

It was previously shown that the Otx2 transcription factor is required not only for photoreceptor cell fate determination but also for the maturation of bipolar cells [30]. The expressions of both *TRPM1-L* and *-S* were not detected in the *Otx2* CKO mouse retina (our unpublished data). This suggests that Otx2 is one of the transcriptional regulators of *TRPM1* in bipolar cells. *TRPM1* is evolutionally conserved from human through *Xenopus tropicalis*. Otx2 is also known to play a role in bipolar cell development from mouse to *Xenopus laevis*. In this regard, it is speculated that *TRPM1* is regulated by Otx2 in ON bipolar cells in an evolutionally conserved manner.

2.3. Temporal and spatial localization of the TRPM1-L channel in retinal development

The temporal and spatial localization patterns of the TRPM1-L protein resemble those of mGluR6. *TRPM1-L* transcripts in retinal bipolar cells begin to be expressed at postnatal day 8 (P8) through P9. Around the stage that retinal cell differentiation is complete, TRPM1-L immunoreactivities were observed diffusely in

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