Phototransduction: Phototransduction in Cones

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Vladimir J Kefalov
Washington University in St. Louis
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Phototransduction: Phototransduction in Cones

V J Kefalov, Washington University School of Medicine, Saint Louis, MO, USA

Glossary

Dark adaptation – The mechanism that allows photoreceptors to recover their sensitivity to dark-adapted levels following exposure to bright light.
Light adaptation – The mechanism that allows photoreceptors to reduce their sensitivity in the presence of steady light.
Phototransduction cascade – A series of reactions in the outer segments of photoreceptors through which the energy of a photon is converted into a change in the membrane potential of the cell.
Visual cycle – A series of reactions initiated by the activation of the visual pigment by light and terminating in resetting the pigment to its inactive, ground state. It involves the decay of the photoactivated visual pigment to free opsin and all-*trans* retinal, the recycling of chromophore from all-*trans* to 11-*cis* outside of photoreceptors, and the regeneration of the visual pigment molecule.
Visual pigment – A G-protein-coupled receptor consisting of protein, opsin, covalently linked to a chromophore, 11-*cis* retinal. The absorption of a photon by the visual pigment is the initial step in activating the phototransduction cascade.

Introduction

Cone photoreceptors mediate our vision during the day and provide us with fine spatial and temporal resolution as well as color perception. In most species, cones are located mostly in the central area of the retina where the image directly in front of the eyes is projected. Unlike rods, where the signal from hundreds of photoreceptors is integrated for optimized photon detection in low light conditions, signals from individual cones are relayed to the brain. As a result, the spatial resolution of our central vision, driven primarily by the cones, is excellent, whereas that of our peripheral vision, driven by the rods, is significantly lower. Color discrimination is achieved as each cone typically expresses a single type of visual pigment which conveys different spectral sensitivity to different cone types. While single photoreceptors cannot discriminate colors as the degree of photoactivation depends not only on the wavelength of the stimulus but also on its intensity, the visual system extracts that information by comparing the signals coming from the different cone types. An interesting exception to the one cell–one pigment rule is the mouse retina where green and ultraviolet cone visual pigments are coexpressed in the same cells. The functional significance of that arrangement is not clear.

Functional Properties of Cones

Cones use a phototransduction cascade, similar to the one well characterized in rods, to convert the energy of light into an electrical signal. In addition, cone phototransduction proteins are homologous, or sometimes even identical, to the ones found in rods. Yet, cones have functional properties that are distinct from those of rods and that are suited for their role as bright-light detectors. First, cones are significantly less sensitive than rods. The rod phototransduction cascade is tuned for high amplification which allows rods to achieve the maximal physically possible sensitivity and generate a detectable single photon response. As such enormous gain requires buildup of the reactions of the phototransduction cascade, the trade-off is the slow kinetics of rod responses. Cones, on the other hand, are 30- to 100-fold less sensitive than rods (**Figure 1**) and require the simultaneous activation of tens to hundreds of visual pigment molecules to generate a detectable response. As a result of the low amplification of their phototransduction cascade, cones are not sensitive enough to function under low light conditions, depriving us of color vision in dim light. Instead, the low cone phototransduction gain shifts their dynamic range toward brighter light conditions and enables cones to function during the day. The low signal amplification in cones is made possible by the rapid inactivation of their phototransduction cascade. This results in the second notable difference from rods, namely, that cone responses are typically several fold faster than rod responses. The rapid activation and subsequent inactivation of the cone phototransduction cascade reactions provides the basis for the high temporal resolution of cone-mediated vision (**Figure 1**). The rapid activation of cones results in short latency of detection, whereas their rapid inactivation enables discrimination of stimuli spaced closely in time. In contrast, the slower rod responses limit the temporal resolution of rod-mediated vision. Third, following exposure to bright light, cones fully recover their sensitivity within a few minutes. Rods, in contrast, experience a long

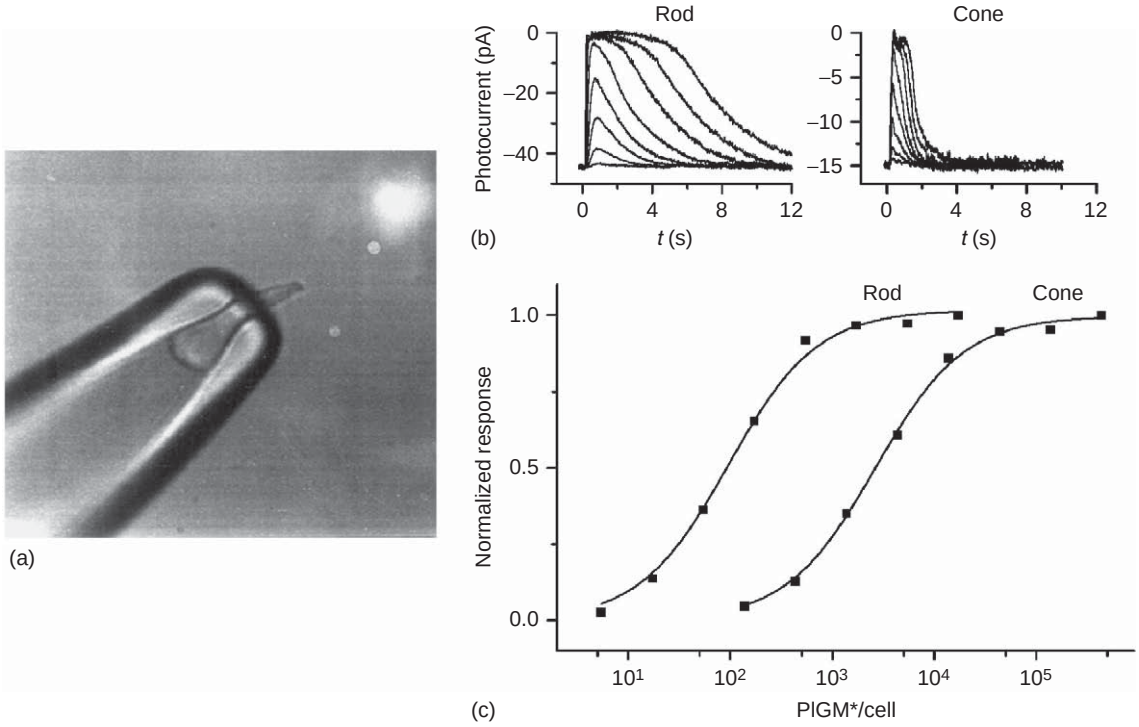

Figure 1 Comparison of rod and cone photoresponses. (a) Salamander red cone drawn in a suction pipet electrode with the outer segment protruding out. (b) Families of photoresponses from a salamander rod (left) and a red cone (right) to brief test flashes of increasing intensity delivered at $t = 0$. Note the significantly faster response kinetics of cone responses compared to rod responses. (c) Normalized intensity–response curves for the same two cells. Note the significantly lower cone sensitivity compared to the rod sensitivity.

refractory period following exposure to bright light and can take up to an hour for a complete recovery of their sensitivity. This process, known as dark adaptation, prevents cones from becoming refractory and allows us to retain visual perception in a quickly changing light environment. Finally, cones have a remarkable ability to adjust their sensitivity over a very wide range and remain photosensitive even in extremely bright light. Rods, in contrast, saturate in even moderately bright light and remain nonfunctional during most of the day. This process, known as light adaptation, prevents cones from saturating in bright light and allows us to see throughout the day. With rods saturated, cones are responsible for most of the visual information reaching our brain during the day. In fact, with the introduction of artificial lighting, humans rely almost exclusively on cones both during the day and at night. This is why cone disorders, such as macular degeneration, the most common cause of blindness in the elderly, have a devastating effect on vision.

Obstacles for Studying Cone Phototransduction

The last several decades have seen a tremendous advance in our understanding of the function of photoreceptors. The development of electrophysiological tools for studying the function of single photoreceptors, together with biochemical and genetic tools have revealed the mechanism of phototransduction and provided quantitative description of the reactions involved in it. Unfortunately, these advances have been almost exclusively limited to rods. The great abundance of rods in most mammalian retinas (95% of all photoreceptors in human and 97% in mouse retinas) has facilitated the purification and biochemical study of rod phototransduction proteins. In contrast, the small fraction of cones and the homology between rod and cone phototransduction proteins have rendered comparable studies from cone proteins technically challenging. A further obstacle has been the fragility of mammalian cone photoreceptors, which has rendered physiological studies from cones also significantly more challenging than comparable rod studies. As a result, while mammalian rod phototransduction has been characterized in quantitative details, most of what we currently know about cone phototransduction is derived from studies of amphibian and fish photoreceptors. Based on the similarities in structure and transduction proteins between rods and cones, it has been assumed that phototransduction in cones follows the same set of reactions as phototransduction in rods. There exist, however, important quantitative phototransduction differences in

rods and cones pertinent to their function in dim and bright light, respectively. The phototransduction cascade in cones will be discussed here in the context of the much better understood rod phototransduction cascade.

In both, rods and cones, phototransduction takes place in specialized compartments, called outer segments, which consist of stacks of membrane disks, similar to a stack of coins. Unlike in rods, where these disks are surrounded by, but not connected to, the plasma membrane, in cones these disks are formed from invaginations of the plasma membrane. As a result, the plasma membrane of cone outer segment has significantly higher area, a factor possibly important for the rapid flow of molecules in and out of the cell. The transduction channels are cGMP-gated nonselective cation channels held open in darkness by the binding of free cGMP in the outer segment. Cone cGMP channels are homologous to those found in rods and in olfactory neurons and consist of two cyclic nucleotide-gated alpha 3 (CNGA3) and two cyclic nucleotide-gated beta 3 (CNGB3) subunits. In darkness, the influx of Na^+ and Ca^{2+} through these channels depolarizes the cells to about −40 mV, which results in the steady release of the neurotransmitter glutamate from the cone synaptic terminal. Photoactivation of the cell results in the hydrolysis of cGMP, closure of the transduction channels, hyperpolarization of the cell, and reduction in the release of neurotransmitter from the cone synaptic terminal.

Cone Visual Pigment and Phototransduction

Phototransduction in cones is initiated by the activation of cone visual pigments by the absorption of a photon. The cone visual pigments, similar to rod pigments, consist of protein, opsin, covalently attached to a chromophore, typically 11-*cis* retinal. Cone opsins have a moderate level (∼50%) of homology to rod opsins. The visual chromophore is a derivative of vitamin A (all-*trans* retinol), which is converted in the pigment epithelium into 11-*cis* retinal and then transported to the photoreceptor's outer segments where it combines with opsin to form the visual pigment. The visual pigment is expressed at very high levels in the disks of the outer segment (3.5 mM), so that a photon traveling along the outer segment has a ∼40% chance of activating a pigment molecule. Interestingly, the concentrations of rod and cone visual pigments in the outer segment as well as their extinction coefficients are similar. In addition, the probability that a pigment molecule will become activated once a photon has been absorbed (quantum efficiency) is also comparable between rod and cone pigments. Thus, with respect to the pigment distribution and optical properties, only the typically smaller size of the cone outer segment compared to that of the rod contributes to the lower sensitivity of cones.

Studies with amphibian photoreceptors indicate that the different stability of rod and cone pigments modulates their respective phototransduction cascades. First, studies of transgenic *Xenopus* rods expressing red cone opsin have allowed the direct observation of physiological responses to the activation of a single cone pigment molecule. This has made possible the determination of the rate of spontaneous thermal activation of red cone pigments, which produces a response identical to the activation by a photon. The molecular rate of thermal activation measured in this way is ∼10 000 times higher for red cone pigment than for rod pigment. As a result, amphibian red cones experience ∼200 pigment activations per second in darkness. This level of dark activity is comparable to the total dark noise measured from salamander red cones, indicating that most of the noise in these cells originates in the thermal activation of the pigment. This spontaneous activity acts as background light to induce adaptation and, therefore, desensitization and acceleration of the flash response. A second mechanism by which the stability of the visual pigment contributes to the differences between rods and cones is based on the covalent bond between opsin and retinal in their respective pigments. Both biochemical and physiological studies indicate that the formation of the covalent bond between opsin and chromophore is reversible in cones but not in rods. As a result, the visual pigment in cones, but not in rods, can spontaneously dissociate into free opsin and 11-*cis* retinal. The very low level of free 11-*cis* retinal in the outer segment (only ∼0.1% of the pigment content) shifts the equilibrium between free and chromophore-bound cone opsin so that even in dark-adapted cones, there is ∼10% free opsin. At this high level, the total catalytic activity of free opsin, though weak per single molecule, is sufficient to induce adaptation and further reduce the sensitivity and accelerate the kinetics of the cone flash responses.

The effects of cone pigment properties on mammalian photoreceptor function have not been well characterized. Interestingly, studies from transgenic mouse rods expressing cone pigments indicate that, though still significantly higher than that of rod pigment, the rate of thermal activation of cone pigment is not high enough to affect cone photosensitivity significantly. A possible explanation for the relatively low thermal activity of cone pigments in mammalian species compared to amphibians might be that they use a slightly different chromophore (11-*cis* retinal or A1) than most amphibian photoreceptors (11-*cis* 3-dehydroretinal or A2). The reversibility of cone pigment formation and its possible effect on cone function have not yet been examined in mammalian cones. Finally, differences in the properties of rod and cone visual

pigment also contribute to the very different rates of dark adaptation in rods and cones.

Activation of Cone Phototransduction

Once activated, the visual pigment binds to and activates a heterotrimeric G protein, called transducin (G_t). This triggers the exchange of GDP for GTP on the α-subunit of transducin ($G_{t\alpha}$) and the dissociation of $G_{t\alpha}$·GTP from $G_{t\beta\gamma}$. This represents the initial amplification step in phototransduction as one visual pigment molecule can activate multiple G_t molecules. Rod and cone transducins are closely related and the primary structures of their α-subunits are ~80% identical, with even higher identity in the region of interaction with the visual pigment. Biochemical studies indicate that rod and cone pigments have comparable binding affinities for rod transducin and that they activate rod transducin with similar kinetics. Furthermore, studies with transgenic animals coexpressing rod and cone visual pigments in the same photoreceptor have shown that rod and cone pigments produce comparable responses. Thus, cone pigments expressed in rods produce a response with rod-like amplification and kinetics and, conversely, rod pigments expressed in cones produce a response with cone-like amplification and kinetics. These results indicate that the activation of the phototransduction cascade by the visual pigment and the inactivation of the visual pigment are not determined by its properties but rather, by the downstream transduction reactions, including the activation of transducin. Indeed, biochemical studies of fish photoreceptors have shown that the activation of transducin is ~25 times less effective in cones compared to rods. This lower activation efficiency would contribute to the lower amplification of the signal and, therefore, to the lower sensitivity of cones. It is not clear yet whether the lower activation of transducin in cones is due to the properties of the cone isoform of transducin or due to the faster inactivation of pigment in cones compared to rods. An interesting recent observation is that exposure to bright light in rods triggers translocation of the subunits of activated transducin from the outer to the inner segment. In contrast, in cones, such translocation does not occur, possibly because transducin subunits are inactivated and re-form a trimer faster than in rods. The mechanism of this light-dependent translocation is still not well understood and is an active area of research.

Once activated by the visual pigment, $G_{t\alpha}$·GTP in turn activates cGMP phosphodiesterase (PDE) by binding to its inhibitory subunit PDEγ and removing its inhibition on the catalytic PDEαβ. The resulting hydrolysis of cGMP by PDE leads to the closure of cGMP-gated channels in the cone outer segment and the hyperpolarization of the photoreceptor to produce the light response. While cone PDE has 60% identity to rod PDE, biochemical studies of fish photoreceptors indicate that the activation of PDE by transducin might also be ~10 times less effective in cones compared to rods, contributing further to the lower cone sensitivity.

Inactivation of Cone Phototransduction

Response termination is achieved as the visual pigment, transducin, and PDE are inactivated and the concentration of cGMP is restored to its dark, preflash level. Though these reactions in cones are not well characterized, it is clear that, similar to their activation, quantitative differences in the inactivation of phototransduction reactions in rods and cones contribute to the lower sensitivity and faster response kinetics of cones. The activity of the visual pigment is initially partially quenched when it is phosphorylated by a G-protein receptor kinase (GRK). Phosphorylation of activated visual pigment is ~50 times faster in cones compared to rods. It appears that this faster phosphorylation is the result of two factors – higher expression of GRK in cones and higher efficiency of cone GRK (GRK7) compared to rod GRK (GRK1). While most species, including human, express GRK1 in rods and GRK7 in cones, the mouse retina is unusual as its rods and cones share the same kinase, GRK1. In this case, the faster pigment inactivation in cones is most likely due to the higher concentration of GRK1 and possibly also to differential modulation of that reaction by the calcium-binding protein recoverin.

Following phosphorylation, complete inactivation of the phosphorylated visual pigment is achieved by the subsequent binding of a protein called arrestin. The cone isoform of arrestin (Arr4) has about 50% identity to rod arrestin (Arr1). The mouse retina again represents an unusual case, as in addition to Arr4, mouse cones also express Arr1. Interestingly, the ratio of arrestin to visual pigment is 7 times higher in cones compared to rods. In dark-adapted rods, most of arrestin is in the inner segment and does not, therefore, contribute to the inactivation of rod visual pigment. As a result, the quantity of arrestin in the outer segments of rods is only a few percent of their visual pigment. Exposure to bright light triggers the translocation of arrestin from the inner to the outer segment for more efficient pigment inactivation. While arrestin also transloactes in cones, the total quantity of arrestin in their outer segments in darkness is comparable to that of their visual pigment. Recent studies from mouse cones lacking both rod and cone arrestins reveal that either arrestin is capable of inactivating cone visual pigment though Arr1 is much more abundant than Arr4 in cones. Studies with transgenic rods expressing cone S-opsin and either rod or

cone arrestin further demonstrate that rod arrestin is more efficient at inactivating cone pigment than cone arrestin. The relatively low expression of Arr4 in cones and its relative inefficiency suggest a possible additional role for this protein. The coexpression of two arrestins and their high concentration in cone outer segments would contribute to the rapid cone pigment inactivation and are consistent with the more rapid pigment inactivation and faster response termination in cones compared to rods.

$G_{t\alpha}$·GTP is inactivated as GTP is hydrolyzed into GDP. This reaction is catalyzed by PDEγ as part of a GTPase-activating protein (GAP) complex that consists, in addition, of regulator of G-protein signaling (RGS9), RGS9 anchoring protein (R9AP), and a G_β subunit ($G_{\beta 5}$). The rod and cone PDEγ have comparable potencies for inhibiting PDE and also for enhancing the hydrolysis of GTP by the GAP complex. In contrast, even though the identical RGS9 protein is present in rods and in cones, its concentration is more than 10 times higher in cones compared to rods. Deletion of RGS9 in the mouse greatly retards cone response inactivation, and mutations in RGS9 have been associated with slow cone deactivation in patients. Thus, while the extent to which the differences in GAP activity in rods and cones contribute to their functional differences is not well understood, RGS9 and the GAP complex clearly play an important role in the inactivation of cone phototransduction.

The final step in photoresponse termination involves the upregulation of synthesis of cGMP by guanylyl cyclase (GC) to restore the concentration of free cGMP in the outer segment and reopen the cGMP-gated channels. While rods express two isoforms of GC, that is, GC1 and GC2, cones appear to express predominantly, if not exclusively, GC1. The role of GC2 in rods is not clear as its deletion produces only a mild change in rod physiology. It is also not understood how modulation of GC by the pair of GC-activating proteins (GCAP1 and GCAP2) contributes to the unique functional properties of cones. Although the distribution of GCAPs between rods and cones in different species is ambiguous, it appears that GCAP2 is prevalent in rods, while GCAP1 is expressed at high levels in cones. The possible role of GCAPs in mediating light adaptation in cones is discussed below in the context of light adaptation.

Dark Adaptation of Cones

Quantitative differences between the phototransduction cascades of rods and cones not only contribute to the difference in sensitivity and kinetics of photoresponses as discussed above, but also play a role for the very different adaptation properties of rods and cones. The ability to recover their sensitivity rapidly following exposure to bright light, or dark-adapt, is critical for the function of cones as daytime photoreceptors. The absorption of a photon by the visual pigment not only triggers its activation, but also results in its eventual decay into free opsin and all-*trans* retinal. Dark adaptation of both, rods and cones, after exposure to bright light requires regeneration of the visual pigment from opsin and 11-*cis* retinal. However, the speed of pigment regeneration, and hence sensitivity recovery, is very different in rods and cones, with full recovery requiring less than 5 min in cones and up to an hour in rods (see **Figure 2**).

Several factors contribute to the rapid pigment regeneration in cones. First, the decay of the photoactivated pigment to free opsin and all-*trans* retinal occurs in seconds for cone pigments compared to minutes for rod pigments. Second, the reduction of all-*trans* retinal into all-*trans* retinol, which takes place in the outer segment and is catalyzed by retinol dehydrogenase (RDH), is also 10–40 times faster in cones compared to rods. The reduction reaction requires the cofactor nicotinamide adenine

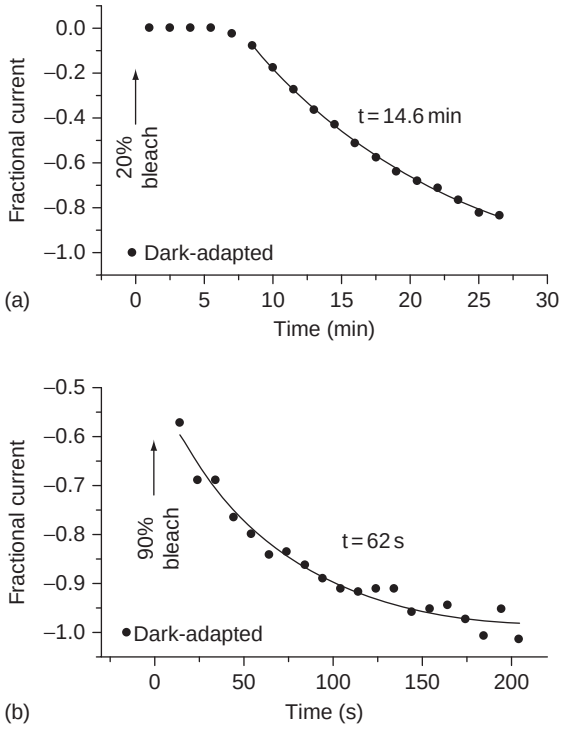

Figure 2 Comparison of rod and cone dark adaptation. Recovery of the circulating (dark) current in salamander rod (a) and red cone (b) measured with a suction electrode. Cells were exposed to bright light that activated (bleached) 20% of the rod pigment and 90% of the cone pigment. The recording was done in the presence of exogenous 11-*cis* retinal to enable pigment regeneration in the isolated cells. Current recovery is fit by a single exponential decay function (solid line). Note the significantly faster recovery of the current in cone compared to the current in the rod.

dinucleotide phosphate oxidase (NADPH). While it is possible that the faster reduction of all-*trans* retinal in cones is due to the different properties of rod and cone RDH enzymes, a more likely hypothesis is that the reduction reaction is limited by the supply of NADPH from the inner segment. Third, single-cell measurements from amphibian photoreceptors indicate that the clearance of all-*trans* retinol from the outer segment is ~25 times faster in cones compared to rods. However, the actual difference in these rates in the intact retina might be affected by factors such as the proximity to the pigment epithelium and the action of extracellular chromophore-binding proteins such as interphotoreceptor retinoid-binding protein (IRBP). Finally, the formation of the covalent bond between opsin and 11-*cis* retinal during pigment regeneration occurs in seconds in cones and minutes in rods. Together, these factors contribute to the faster turnover of cone visual pigment and the faster dark adaptation of cones compared to rods.

In addition to the effects of faster visual pigment decay and regeneration, cone dark adaptation is accelerated by the noncovalent interaction between opsin and 11-*cis* retinal. Pigment regeneration requires the initial binding of 11-*cis* retinal in the chromophore pocket of free opsin. While in rods, the noncovalent binding of retinal activates the opsin molecule and desensitizes the rods, in cones, this reaction has the opposite effect and inactivates cone opsin. As a result, the noncovalent binding of 11-*cis* retinal to opsin delays dark adaptation in rods but accelerates it in cones, as it allows cones to substantially recover their sensitivity even before the regeneration of their visual pigment.

Recent biochemical studies indicate that another mechanism contributing to the faster dark adaptation of cones compared to rods is based on the supply of recycled chromophore for pigment regeneration. The canonical visual cycle involves the pigment epithelium, where all-*trans* retinol is converted into 11-*cis* retinal via a series of enzymatic reactions and then transported back to the photoreceptors for incorporation into opsin. The rapid dark adaptation of cones and their ability to maintain adequate levels of pigment and remain light sensitive even in steady bright light require rapid pigment regeneration, hence rapid recycling of chromophore for cones. However, the slow rate of chromophore turnover in the pigment epithelium and the competition for recycled chromophore between cone opsin and overwhelming levels of rod opsin in most rod-dominant species indicate that the canonical pigment epithelium visual cycle might not be sufficient to meet the chromophore demand of cones. Indeed, recent biochemical studies from cone-dominant species have brought up the idea of a second, cone-specific pathway for recycling of chromophore located within the retina and possibly relying on the Müller cells. The role of this novel cycle in mammalian rod-dominant species is still controversial. However, recent physiological experiments with amphibian photoreceptors demonstrate the function of a retina visual cycle under physiological conditions in a rod-dominant retina. Importantly, the combined action of the pigment epithelium and the retina visual cycles is required for the rapid and complete dark adaptation of cones.

Light Adaptation in Cones

In contrast to rods, which saturate in moderate light and are not responsive during the day, cones have the ability to adapt their sensitivity and remain functional over a very wide range of light intensity. Studies with amphibian and fish photoreceptors indicate that, similar to the case of rods, cone adaptation is mediated by intracellular calcium, modulated by the activation of the phototransduction cascade. In the dark, the continuous current entering the outer segment through the cGMP-gated channels is carried in part by calcium, which is returned to the extracellular space via a $Na^+/(Ca^{2+}, K^+)$ exchanger. Following photoactivation and the closure of cGMP channels, calcium continues to be exported out of the cell through the $Na^+/(Ca^{2+}, K^+)$ exchanger until a new equilibrium is reached. As a result, activation by light causes a decline in the concentration of calcium in the outer segment of the cell. This triggers the calcium-mediated negative feedback on phototransduction, which in rods is required for eventually terminating the signal and for adapting the cell in response to light. Interestingly, calcium constitutes a larger fraction of the total ionic flux in and out of the outer segment of cones compared to rods. Thus, in cones of amphibians and fish, the fraction of photocurrent carried by calcium is about 35% compared to 20% in rods. As would be expected from the need to maintain a steady calcium concentration in darkness, the matching rates of extrusion of calcium via the $Na^+/(Ca^{2+}, K^+)$ exchanger are also higher in cones compared to rods. The combination of faster turnover of calcium in cones and their smaller volume compared to rods allows calcium in cones to decline several times faster upon light stimulation. In addition, their range of calcium concentrations from darkness to bright light is threefold wider than that in rods. These quantitative differences create the potential for more powerful modulation of phototransduction by calcium in cones compared to rods consistent with the ability of cones to adapt better and faster to various light conditions than rods.

The mechanisms by which calcium modulates the cone phototransduction cascade are not well understood. However, comparison between cone and rod phototransduction reveals several interesting points. One mechanism by which calcium modulates phototransduction in rods involves inactivation of the visual pigment via

phosphorylation by rhodopsin kinase. This reaction is modulated by the calcium-binding protein recoverin (also known as S-modulin). Recoverin is a member of the EF-hand superfamily and exerts its effect by inhibiting phosphorylation of rhodopsin by rhodopsin kinase at high calcium levels. In rods, inhibition of rhodopsin kinase by recoverin regulates phototransduction in darkness, in high calcium conditions, but has little effect during light adaptation, in low calcium conditions. The role of recoverin in modulating cone phototransduction in darkness and during light adaptation is not known. However, rods and cones share the same isoforms of recoverin and rhodopsin kinase. In addition, calcium modulates the sites and extent of pigment phosphorylation in cones but not in rods. Finally, unlike in rods, in cones, the calcium-dependent inactivation of cone visual pigment could be the rate-limiting step for the shutoff of the cone photoresponse.

Another mechanism by which calcium modulates phototransduction in rods involves the synthesis of cGMP by GC. As discussed above, this reaction is modulated by GCAP1 and GCAP2. GCAPs modulate GC in rods up to 20-fold as they inhibit it at high intracellular calcium levels and activate it at low calcium levels. While the simultaneous deletion of GCAP1 and GCAP2 delays the recovery of cone light responses, the extent to which GCAPs modulate cone phototransduction in darkness and during light adaptation is not known.

Finally, calcium is also believed to directly modulate the cGMP-gated channels in cones. The Ca^{2+}-dependent modulation of cGMP current is minimal in amphibian and undetectable in mammalian rods. In contrast, cone cGMP channels are directly modulated by Ca^{2+} both in fish and in mammalian retina. The molecular mechanism of cone channel modulation remains to be discovered. While calmodulin binds to and modulates heterologously expressed cGMP-gated channels, its role in the intact cone photoreceptor has been questioned.

Epilog

These are exciting times for studying cone phototransduction. Until recently, technical issues such as the low abundance of cone photoreceptors in rod-dominant retinas and the fragility of mammalian cone photoreceptors have held back the biochemical and physiological studies of cones. As a result, despite the crucial role of cones for our daytime vision, mammalian cone phototransduction has been poorly understood. Recent development of several genetically modified mice has turned the tables. One example is the Nrl knockout mouse. Nrl is a transcription factor required for rod photoreceptor differentiation and its deletion produces a retina populated exclusively by cone-like photoreceptors. This makes possible the purification and biochemical characterization of mammalian cone phototransduction proteins. The Nrl knockout retina has also been used recently for physiological studies of cone photoreceptors. Other examples of useful genetically modified mice include those lacking the rod visual pigment (rhodopsin knockout) and the rod $G_{t\alpha}$ subunit (transducin α knockout). The lack of functional rods in both of these retinas makes possible the physiological identification and study of cone photoreceptors. This approach was most recently used to investigate the role of Arr1 and Arr4 in the inactivation of mouse cone pigments. The combination of new genetic models and improved physiological tools provides promise for studies of mammalian cone photoreceptors using the full range of tools that have been so successful in characterizing the function of mammalian rods. This should allow not only quantitative characterization of the cone phototransduction cascade but also understanding the mechanisms for cone dark and light adaptation which make cones invaluable as our daytime photoreceptors.

See also: Light-Driven Translocation of Signaling Proteins in Vertebrate Photoreceptors; Phototransduction: Adaptation in Cones; Phototransduction: Adaptation in Rods; Phototransduction: Inactivation in Cones; Phototransduction: Inactivation in Rods; Phototransduction: Phototransduction in Rods; Phototransduction: Rhodopsin; Phototransduction: The Visual Cycle.

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