Commentary

Photoreceptor Light Adaptation: Untangling Desensitization and Sensitization

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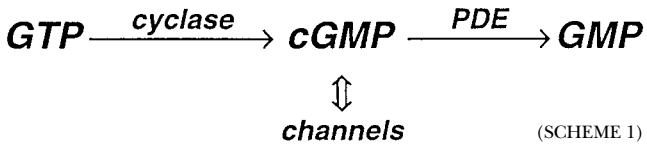
The illumination at the earth's surface varies by >10 orders of magnitude during the normal day–night cycle, and the vertebrate visual system covers this entire range of light intensities with two neuronal subsystems that rely on the activity of two types of photoreceptor cells, rods and cones. Human rod vision operates over approximately seven decimal orders of illumination. The cone visual system operates over an even wider range (Rodieck, 1998). Light adaptation occurs at all levels of the visual system, from photoreceptors to central neurons. Yet, the function of the entire visual system depends on the ability of the photoreceptors themselves to adjust their sensitivity to the ambient lighting situation. Thus, photoreceptors must generate reliable signals at night when single photons are captured between long intervals of darkness, and must also continue to signal at the very high light intensities encountered on a sunny day. Photoreceptor light adaptation is likely to be mediated by multiple and perhaps redundant molecular mechanisms (Detwiler and Gray-Keller, 1992; Lagnado and Baylor, 1992; Bownds and Arshavsky, 1995; Pugh et al., 1999). Recently, Pugh et al. (1999) summarized nine individual molecular mechanisms thought to be involved in adaptation and discussed their relative contributions to the entire adaptation process. A study by the same authors, published on page 795 (Nikonov et al., 2000, this issue), provides the experimental support for their insights and further develops a theoretical framework that will impact future studies of photoreceptor light adaptation.

The molecular mechanisms underlying light adaptation may be discussed in the context of the reactions governing cGMP in the photoreceptor cytoplasm (Hodgkin and Nunn, 1988):



(SCHEME 1)

The intracellular concentration of cGMP is determined by the rate of its synthesis by the guanylyl cyclase and the rate of its hydrolysis by the cGMP phosphodiesterase (PDE). This concentration is constantly monitored by the cGMP-gated channels located in the photoreceptor plasma membrane. In the dark-adapted photoreceptor, a steady cGMP concentration of a few micromolars is maintained. This keeps a fraction of the cGMP-gated cationic channels of the outer plasma membrane open and the cell depolarized. Light causes cGMP to fall by activating PDE via the enzymatic cascade including photoactivated rhodopsin, the G-protein called transducin, and the effector enzyme PDE. The reduction in the cGMP concentration results in channel closure and photoreceptor hyperpolarization. Recovery of the light response occurs when the excitatory cascade is inactivated, cGMP level is restored by guanylyl cyclase, and the channels reopen. During photoresponse, the intracellular Ca^{2+} concentration also declines since its entry through the cGMP-gated channels is blocked while it continues to be extruded by a Na^{2+}/Ca^{2+}-K^+, exchange molecule located in the plasma membrane. It is this Ca^{2+} decline that has been implicated as the main factor underlying light adaptation because it leads to the feedback regulation of various phototransduction cascade components.

To illustrate the importance of light adaptation to normal photoreceptor function, consider the following. For rod photoreceptors to register minimal light stimuli, a high degree of signal amplification has to be achieved in the rhodopsin-transducin-PDE cascade. For example, at the peak of the toad rod response to a single photon, which occurs ~1 s after photon absorption, ~5% of the open, light-sensitive channels become closed. This implies that steady illumination delivering only ~100 photons per second would close all of the channels, rendering the cell unresponsive to any further light stimulation. But because rods adapt to light, this saturation is avoided until the ambient illumination produces a photon capture rate of ~10,000 photons per second. The effect of adaptation is even more profound in cones: they virtually never saturate.

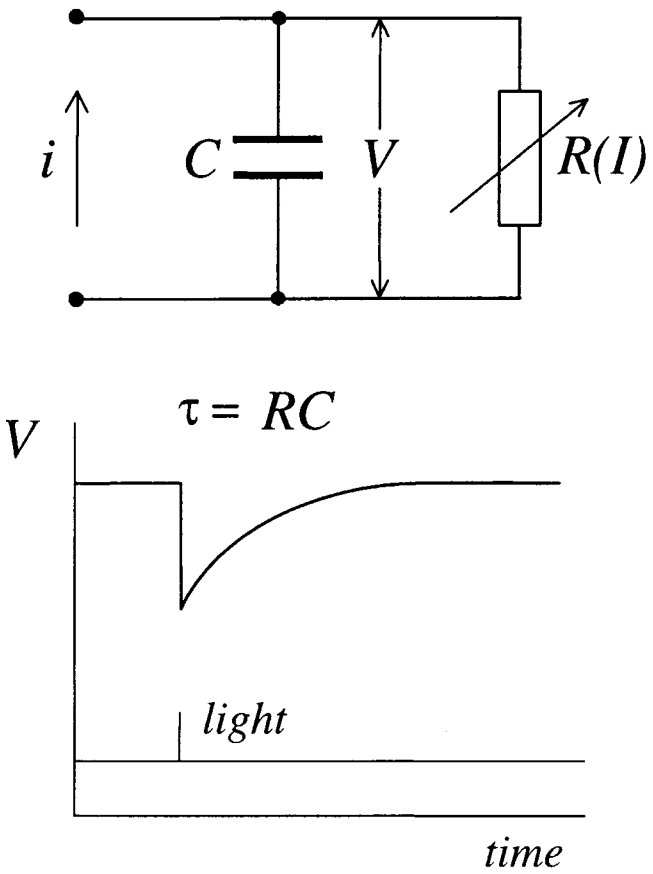
The transition between the dark- and the light-adapted states of the photoreceptor is accompanied by

J. Gen. Physiol. © The Rockefeller University Press • 0022-1295/2000/12/791/4 $5.00
Volume 116 December 2000 791–794
http://www.jgp.org/cgi/content/full/116/6/791

two significant changes in the physiological properties of photoreceptors. First, light-adapted photoreceptors are less sensitive to light, preventing them from becoming blind at high light intensity levels. Second, light-adapted photoreceptors produce quicker photoresponses, improving the temporal resolution in the visual system. It is to these two features that the term "light adaptation" has been most often applied, and the prevailing view in the literature suggests that the Ca^{2+} feedback systems underlie both. One immensely important contribution of Nikonov et al. (2000) is to challenge this view. The authors examined the process of light adaptation in salamander rod photoreceptors and provide experimental evidence that both photoreceptor desensitization and response acceleration are largely independent of Ca^{2+} feedback. Instead, they result from the elevated PDE activity caused by steady background illumination.

One effect of steady PDE activation on the absolute response sensitivity is rather straightforward. Since the absolute sensitivity of the response is proportional to the absolute number of the channels open before the flash, the reduction in the number of open channels caused by the steady illumination automatically leads to a compression of the response amplitude. However, the response compression is a relatively small part of the total effect of steady PDE activation. The main source of flash sensitivity reduction is due to acceleration of signal recovery caused by the PDE activation. Formally, this acceleration occurs because the time constant of the reaction governing flash-induced cGMP change is inversely proportional to the specific PDE activity per cytoplasmic volume. This time constant is exactly the same time constant that governs the turnover of the entire cGMP cytoplasmic pool under the same illumination conditions.

The latter concept is not intuitive, and Nikonov et al. (2000) provide a hydrodynamic "bathtub" analogy to illustrate this effect in the DISCUSSION of their paper. We provide another analogy that might appeal to the reader familiar with the properties of electrical circuits. Consider an electrical circuit consisting of a variable resistor, a capacitor, and a constant current source. The voltage (V) across the capacitor represents the cGMP concentration. The current (i) that charges the capacitor (C) represents the rate of cGMP synthesis by guanylyl cyclase (α, according to Nikonov et al., 2000), while the capacitor represents the cell volume. PDE activity is represented by the variable resistor ($R(I)$), which is regulated by light (I). The conductivity of the resistor, $1/R$, represents the sum of the dark basal PDE activity and the light-stimulated PDE activity. The voltage across the capacitor is set by the balance between the current inflow in the circuit and the leakage through the resistor. The equations that describe the changes of the voltage in the circuit are identical to those describing the dynamics of the cGMP concentration in the rod.



(SCHEME 2)

In this analogy, a flash response is represented by the introduction of a brief, transient decrease in $R(I)$. This causes the voltage to drop to a certain level, and then it exponentially returns back to the steady level with a time constant $\tau = RC$. Since $1/RC$ is equivalent to the ratio of the steady state activity of PDE to the cytoplasmic volume (β, according to Nikonov et al., 2000), RC represents the time constant of the exchange of the cGMP cytoplasmic pool. Then it is clear that a higher steady PDE activity reduces this time constant and leads to faster recovery of cGMP to its baseline level. Nikonov et al. (2000) demonstrate that this second kinetic effect of the steady pre-flash PDE activity is the main factor responsible for the acceleration of the photoresponse during light adaptation. It is important to note that since the circuit is linear, the time course of the "flash" response recovery is independent of the steady value of the current i. Changes in i simply scale the amplitude of the voltage (cGMP) response without altering its characteristic recovery time. Thus, the level of the steady state cyclase activity, i in this analogy, has no bearing on the rate of the photoresponse recovery.

The accelerated recovery means that the flash response develops over a shorter period of time, and this reduces the sensitivity to a flash superimposed on a steady background. Thus, the steady state PDE activation reduces the sensitivity of the photoreceptor by the combined effects of reducing the fraction of open channels and by cutting the photoresponse short. Elegant experiments allowed Nikonov et al. (2000) to quantify the degree of PDE activation by steady background lights. They show that, of the ~100-fold reduction in the flash sensitivity observed with their brightest background intensities (see Fig. 6 in Nikonov et al., 2000), ~5-fold is due to the response compression and ~15-fold is due to the kinetic effect of PDE activation, with the residual likely due to the effect of recoverin acting on the activated rhodopsin lifetime.

Having attributed the major portion of the reduction in photoreceptor sensitivity and the acceleration of the photoresponse to the elevated PDE activity before the flash, the question arises: what role does Ca^{2+} feedback play in light adaptation? The answer is clear when we keep in mind that the steady PDE activity produced by the background light causes a substantial increase in the cGMP hydrolytic activity. If there were no compensating mechanisms, cGMP concentration would be dramatically reduced, even under moderate background illumination, eventually leaving no channels open to register further light changes. Thus, the most fundamental role of Ca^{2+} in light adaptation is to oppose this saturation by engaging a number of molecular mechanisms that ultimately lead to the reopening of channels and, therefore, to the extension of the range of light intensities over which the photoreceptor operates (see Pugh et al., 1999 for references and detailed discussion).

The major range-extending effect of Ca^{2+} is mediated by a feedback onto guanylyl cyclase through the Ca^{2+} binding proteins called guanylyl cyclase activating proteins. Light-dependent Ca^{2+} decline causes an increase in the rate of cGMP synthesis that counteracts the elevated steady PDE activity during background illumination. This effect of steady background light should not be confused with the dynamic Ca^{2+} feedback on guanylyl cyclase during the flash response that speeds up the flash response recovery. Nikonov et al. (2000) argue that the effect of dynamic cyclase activation varies little with background light conditions and, thus, should not be considered as an important factor in light adaptation.

The second range-extending effect of Ca^{2+} targets the cGMP-gated channels directly. Ca^{2+} decline causes the channels to become more sensitive to cGMP, so that they operate at lower cGMP concentration. This effect is likely mediated by calmodulin or calmodulin-like proteins, and appears to be more significant in cones than in rods (Rebrik et al., 2000). Both of these effects lead to the reopening of cGMP-gated channels during steady illumination without causing any desensitizing effects; instead, they resensitize the photoreceptor.

The third Ca^{2+} feedback differs from the others because it causes both a range extension and contributes to the desensitization of the cell. Ca^{2+} decline enhances rhodopsin phosphorylation through the Ca^{2+}-binding protein recoverin, leading to a decrease in the lifetime of the activated rhodopsin. This results in desensitization because it reduces the number of PDE molecules activated by each rhodopsin. The operating range is also extended because the reduced number of active PDEs translates into a reduced steady cGMP hydrolytic rate. Both Nikonov et al. and other recent literature discussed by the authors demonstrate that, in rods, this mechanism appears to be much less potent than the feedback onto the guanylyl cyclase.

Another important result reported in the their article is that there is no indication of a fourth proposed Ca^{2+} feedback mechanism, the adaptive regulation of the gain in the cascade between rhodopsin activation and channel closure. Lamb and Pugh (1992) developed a method for estimating the gain in the phototransduction cascade from analyzing the initial rising phase of flash responses. Later, other investigations discussed by Nikonov et al. (2000) showed that this slope was decreased for flashes presented during background illumination or while intracellular Ca^{2+} was artificially reduced in darkness, concluding that this reflected a Ca^{2+} feedback system that reduced cascade gain during light adaptation. In the current paper, Nikonov et al. (2000) show that for background light intensities that close up to 80% of the light-sensitive channels and result in an approximate fivefold reduction in intracellular Ca^{2+}, the very initial rising phase of flash responses, in fact, is not changed. They conclude that the apparent reduction in the amplification induced by background light or lowered intracellular Ca^{2+} described in the literature is likely due to the increased steady level of PDE activity and increased rate of photoexcited rhodopsin quenching that cause the photoresponse to peel off from an invariant initial trajectory at very early times.

Nikonov and colleagues now put forth the view that Ca^{2+} feedback in light adaptation serves almost exclusively to increase photoreceptor sensitivity rather than as a mechanism of photoreceptor desensitization. Although this may sound paradoxical, the sensitizing effect of the Ca^{2+} feedback–mediated range extension was evident from the very first publications that demonstrated the importance of light-induced Ca^{2+} decline for light adaptation (Matthews et al., 1988; Nakatani and Yau, 1988). In these studies, inhibiting Ca^{2+} feedback during steady background illumination caused a catastrophic reduction of flash sensitivity. Ca^{2+} feed-

back largely prevented the sensitivity loss and extended the operating range of the photoreceptor by ~100-fold (see Figure 2 in Matthews et al., 1988). The elegance of the Nikonov et al. (2000) article is that they found a clear way to disentangle the roles for both desensitizing and sensitizing mechanisms in the overall adaptation process.

This brings us back to the definition of light adaptation in photoreceptors. As we mentioned above, adaptation is usually defined as a combination of cell desensitization and response acceleration. The logic of Nikonov et al. (2000) suggests that it is necessary to redefine adaptation to encompass three interrelated phenomena: cell desensitization, response acceleration, and operating range extension. Individual molecular mechanisms may contribute to one or more of these three features. As outlined by Pugh and colleagues (1999), desensitization in rods involves an increase in steady cGMP hydrolysis, signal compression, and a decrease in rhodopsin lifetime by Ca^{2+}/recoverin. Response acceleration involves an increased steady cGMP hydrolysis and a decrease in rhodopsin lifetime. Range extension involves three Ca^{2+}-dependent processes: an increase in cGMP synthesis; an increase in cGMP sensitivity of the channels; and a shortening of the lifetime of photoactivated rhodopsin.

Nikonov et al. (2000) provide a detailed mathematical model of vertebrate rod phototransduction and light adaptation based upon virtually all well established biochemical mechanisms. Modeling of this sort naturally includes many parameters that leave a lot of room for ambiguity when fitting responses. However, in the current and in a previous article, Nikonov and colleagues (Nikonov et al., 1998, 2000) have experimentally estimated many of the key physiological and biochemical parameters independently. This almost completely eliminates arbitrary manipulation of the parameters and increases the robustness of the conclusions drawn from the model.

With the quantitative description of phototransduction and light adaptation that Nikonov et al. provide, what is left unknown? We provide the following three examples here. First, although Nikonov et al. found no evidence for regulation of the phototransduction gain under their experimental conditions, it remains to be seen whether or not gain regulation occurs at higher illumination levels, on a longer time scale, or in different species. If it does, it would imply the existence of additional biochemical mechanisms and molecular components that are not included in the present scheme of phototransduction. Second, little is known about the molecular mechanisms that underlie light adaptation in cones. Cones are able to cover a wider range than rods, and are virtually impossible to saturate with continuous background light. Future studies should be directed towards understanding if the entire cone adaptation could be accounted for by perhaps more efficient rod-like adaptation mechanisms, or if it requires additional unique mechanisms. Third, on a higher level of the visual processing, it is unknown how adaptation of individual photoreceptors contributes to adaptation of the entire visual system. It remains to be determined how any of the three components of photoreceptor light adaptation, cell desensitization, response acceleration, and sensitivity range extension, may cause our light-adapted vision to work faster, with better contrast sensitivity and higher spatial resolution.

Submitted: 27 October 2000
Revised: 30 October 2000
Accepted: 30October 2000

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