Letter to the Editor

Transduction Gain in Light Adaptation of Rod Photoreceptors

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Nikonov et al. (2000) recently reported a study of light adaptation in salamander rod photoreceptors. Analysis of their experimental data has led these investigators to conclude that elevation of the level of activated cGMP phosphodiesterase (PDE*) by background light, with a resulting decrease in the effective lifetime of cGMP, is the primary mechanism responsible for noncompressive desensitization of the flash response. They further conclude that this desensitization involves little if any reduction in signal amplification within the early, activating reactions of the transduction cascade. One aim of the present Letter is to note the primary dependence of background desensitization on a process, termed “gain” reduction below, that is distinct from PDE* elevation (reduced cGMP lifetime). A second aim is to point out that the Nikonov et al. (2000) data leave open the possibility that the desensitization depends strongly on reduced amplification within the chain of activating reactions.

The study by Nikonov et al. (2000) involved the analysis of photocurrent flash responses obtained during steady background illumination. Fig. 1 reproduces the data shown in Fig. 2 of Nikonov et al. (2000), which illustrates responses of a single rod to a fixed series of test flashes presented in darkness, and in background light of strengths estimated at 260, 810, and 2,600 phototransduction diskdisk per second. Consecutive increases within the fixed series of test flash strengths were about threefold (see Fig. 1 legend). A–C of Fig. 1 compare the family of dark-adapted responses with each of the three families of responses obtained in background light. Here the light-adapted data have been shifted vertically as a group to match the maximal, saturating amplitude of the light-adapted response with that of the dark-adapted response. As photocurrent saturation represents the invariant (i.e., background-independent) condition of essentially zero circulating current, such a match allows evaluation of the total response, i.e., the response to the test flash plus steady background, associated with a given test flash under dark-versus light-adapted conditions.

Both amplification within the disk-based, activating reactions of transduction (i.e., the reactions that link photon absorption with PDE* generation) and the kinetics of shut-off of the activated intermediates (activated rhodopsin, activated transducin, and PDE*) determine transduction “gain”, a parameter that describes the efficiency of signal transmission within the disk-based transduction stages. The contribution of a gain reduction to background desensitization has been considered in a previous study (Pepperberg et al., 1994). Following with somewhat different terminology the approach previously described (Eqs. 5 and 6 and accompanying text of Pepperberg et al., 1994), we consider a simple mechanism in which background light produces a static decrease in phototransduction gain. Defining g as the relative gain (0 < g ≤ 1) and g = 1 under dark-adapted conditions, a similarity between the dark-adapted response to a test flash of strength I₀ and the total light-adapted response obtained with a test flash of strength I₀ is predicted when I₀ and I₀ satisfy the relation

\[ I₀ = g (I₀ + I_b \tau_{eff}), \]  

where I₀ is the background strength, \( \tau_{eff} \) is an effective integration time, and the product (g I₀ \( \tau_{eff} \)) is the effective excitation associated with the maintained response to the background itself. That is, when I₀ and I₀ satisfy Eq. 1, the total response associated with I₀ is predicted to overlay, or “cap”, that generated by I₀. Note that g, as defined here, is a measure of noncompressive gain (albeit different from the relative fractional sensitivity defined in Eq. 8 of Nikonov et al., 2000), in that maximal excursions of the total response in background light and in darkness are identical.

Fig. 1 A illustrates responses obtained in darkness and in the presence of the 260 \( \Phi \) s⁻¹ background. For the brighter test flashes, where I₀ is expected to greatly exceed the flash-independent term (I₀, \( \tau_{eff} \)), inspection of Fig. 1 A indicates a similarity between the light-adapted total response obtained at a given flash strength and the dark-adapted response obtained with the next weaker flash in the tested series (responses labeled L and D, respectively). The relationship is consistent with represen-
tation of the effect of the 260 $\Phi$ s$^{-1}$ background as a gain reduction from unity to a value slightly greater than 1/3; i.e., slightly greater than the ratio of the investigated flash strengths ($I_f^D / I_f^L$) that yield the near match of the responses (Eq. 1). Furthermore, the light-adapted total response obtained with a weaker flash ($\Phi$ = 830; response labeled *L in Fig. 1 A) somewhat exceeds the dark-adapted response to a flash of $\approx$1/3 this strength ($\Phi$ = 260; response labeled *D); the ratio $I_f^D / I_f^L$ needed for a near match appears to exceed $\approx$1/3. This is consistent with Eq. 1; i.e., with $g = I_f^D / (I_f^L + I_{b\tau_{ef}}) \approx 1/3$, for the case that $I_f^L$ is comparable to or smaller than ($I_b \tau_{ef}$). A similar relationship is evident in Fig. 1 B, where responses obtained with the 810 $\Phi$ s$^{-1}$ background are compared with those obtained in darkness. Here, the apparent light-adapted gain inferred from the bright flash responses is slightly less than 1/3; as in panel A, the ratio $I_f^D / I_f^L$ required for a near match of dark- and light-adapted total responses appears to increase at relatively low $I_f^L$, which is consistent with Eq. 1. The relationship evident in Fig. 1, A and B, is consistent also with that in D, which compares total responses obtained at 810 and 260 $\Phi$ s$^{-1}$. Panels C, E, and F of Fig. 1 compare total responses obtained at 2,600 $\Phi$ s$^{-1}$ with those obtained in darkness (C), at 260 $\Phi$ s$^{-1}$ (E), and at 810 $\Phi$ s$^{-1}$ (F). Inspection of the bright flash responses in these panels suggests a gain of about 1/5 at 2,600 $\Phi$ s$^{-1}$. Furthermore, Fig. 1 (D–F) shows that increasing the background strength from 260 $\Phi$ s$^{-1}$ to 810 or 2,600 $\Phi$ s$^{-1}$ has a comparatively small effect on the size and kinetics of the total response obtained with a relatively weak flash (i.e., in D–F, the illustrated total responses at $\Phi$ = 2,600 are similar).

Fig. 5 A of Nikonov et al. (2000) shows normalized response functions for the rod described in the present Fig. 1. Inspection of Fig. 5 A (Nikonov et al., 2000) indicates sensitivities, relative to the dark-adapted value (based on the rightward shift of the response function), of 1/4.1, 1/5.7 and 1/12.7, respectively, with backgrounds of 260, 810, and 2,600 $\Phi$ s$^{-1}$. At each background, the gain reduction inferred from the bright-flash responses (reductions in gain to slightly more than 1/3, slightly less than 1/3, and about 1/5, respectively; see above) thus represents a major contribution to the overall measured desensitization of the response function.

In summary, the above analysis of the Nikonov et al. (2000) data shows that a gain decrease of the type considered in Eq. 1 accounts, to a first approximation, for the effect of background light on the flash response. There is no doubt that the light-induced elevation of PDE* activity and the resulting effective decrease in
cGMP lifetime influence the size and time course of the flash response both in darkness and in background light. However, the present analysis and the generally similar results reported by Pepperberg et al. (1994) imply that this process is secondary to a reduction in gain as a contributor specifically to noncompressive background desensitization.

The conclusion by Nikonov et al. (2000) that reduced amplification plays little or no role in light adaptation is based centrally on the finding, by these investigators and others (e.g., Torre et al., 1986), that background light has no significant desensitizing effect on the initial segment of the normalized flash response. However, both the absence of desensitization in the initial segment of the normalized response, and a major contribution of reduced gain to overall desensitization, can be explained by a mechanism in which background light acts to reduce the probability of (i.e., block) a delayed activating transition of photoactivated rhodopsin and, thus, produce a delayed reduction in amplification (Pepperberg, 1998). This hypothesized mechanism is generally consistent with a substantial body of experimental data (studies cited in Pepperberg, 1998) including the Nikonov et al. (2000) results considered here. That is, in the Pepperberg (1998) model, expression of a reduced instantaneous gain in the light-adapted flash response is predicted to develop at post-flash times near and beyond \( \tau \approx 150 \text{ ms} \), which is the hypothesized characteristic time of the activating rhodopsin transition that is blocked by the action of background light.

In conclusion, the mechanistic points at issue may be summarized as follows. There is general agreement that contributors to noncompressive background desensitization could in principle include the following: (1) reduced amplification within the chain of activating reactions; (2) shortened lifetime of one or more of the activated disk-based intermediates; and (3) elevated PDE* activity and consequent reduction in effective cGMP lifetime. Mechanisms of type 1 include: (1a) a reduction in amplification that is operative at the earliest measured times in the flash response, i.e., at post-flash times of \( \tau \approx 1 \text{ ms} \) and beyond; and (1b) a delayed reduction in amplification, i.e., due to interruption of an activating reaction that begins at times long after \( \tau \approx 1 \text{ ms} \). Nikonov et al. (2000) interpret their results to suggest that 3 is the primary mechanism of noncompressive desensitization, 2 is secondary, and 1a is negligible. The present interpretation, which is based on the studies by Pepperberg et al. (1994) and by Pepperberg (1998), suggests that 1b (specifically, blockage of a delayed rhodopsin activating transition) is the primary mechanism and 3 is secondary.

REFERENCES


