Principles and Practice of Clinical Electrophysiology of Vision

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Suppressive Rod-Cone Interaction

Thomas E. Frumkes

Rod- and cone-vision do not operate independently: cone-mediated pathways are tonically inhibited by dark-adapted rods. This latter phenomenon is referred to throughout this article as *suppressive rod-cone interaction (SRCI)*, although other names have been used in the literature.

BACKGROUND

SRCI was discovered by four independent psychophysical investigations of flicker.[2, 14, 27, 34] Sensitivity to cone-mediated flicker *decreases* during the rod-recovery phase of dark adaptation (e.g., see Fig 59–1); similarly, cone-mediated flicker sensitivity *increases* as the illuminance of rod-stimulating backgrounds increases (e.g., see Fig 59–2). Action spectra showed SRCI to reflect an influence of the dark-adapted state of rods upon cone-mediated vision.[2, 26] Furthermore, this effect clearly reflects a tonic inhibitory influence of dark-adapted rods, not a facilitatory effect produced by light-adapted rods (see below).

SRCI has been documented by electroretinographic (ERG) procedures in normal humans.[6] The technique is quite difficult, and psychophysical procedures are much more fruitful for clinical investigation. However, our knowledge of this effect is considerably enhanced by intracellular recordings in subhuman species. SRCI has been clearly documented in cat horizontal cells and has been observed in all types of neurons in the amphibian retina except rods and color-opponent cells.[21, 29, 40] In the mud puppy, SRCI is blocked in *all* retinal neurons by divalent ions such as lead, which selectively block the rod input to second-order neurons, or by excitatory amino acid analogues such as D-*O*-phosphoserine, which selectively block the light response of horizontal cells; in the presence of such agents, cone-mediated flicker responses are considerably *enhanced*.[18, 22] This strongly suggests that SRCI reflects a tonic *inhibitory* influence of dark-adapted rods upon cone pathways that is synaptically mediated by horizontal cells.

In the mud puppy, SRCI is seen in the cones themselves and is again blocked when horizontal cell responses are prevented pharmacologically, thus suggesting that SRCI must partially reflect a direct inhibitory influence upon cones. In amphibians, SRCI can be modified by the application of either agonists or antagonists of the putative neurotransmitter substances γ-aminobutyric acid (GABA), glycine, or dopamine[19, 20, 44]; however, these substances do not really mimic or totally block SRCI. In summary, the neurotransmitter(s) as well as the specifics of the neural pathway underlying this horizontal cell–mediated influence are at present unclear. It is clear that SRCI reflects one or several different rod-modulatory influences upon cone pathways within the retinal outer plexiform layer.

When using either psychophysical or neurophysiological procedures, SRCI has been shown to be limited by three parameters.[10, 21, 27, 40] First, SRCI is very small with low-frequency flicker, but increases to a >1 $\log_{10}$ effect with flicker frequencies >15 Hz. Second, background enhancement of flicker increases with illuminance of the background field up to a limiting value. In the cat, human, and mud

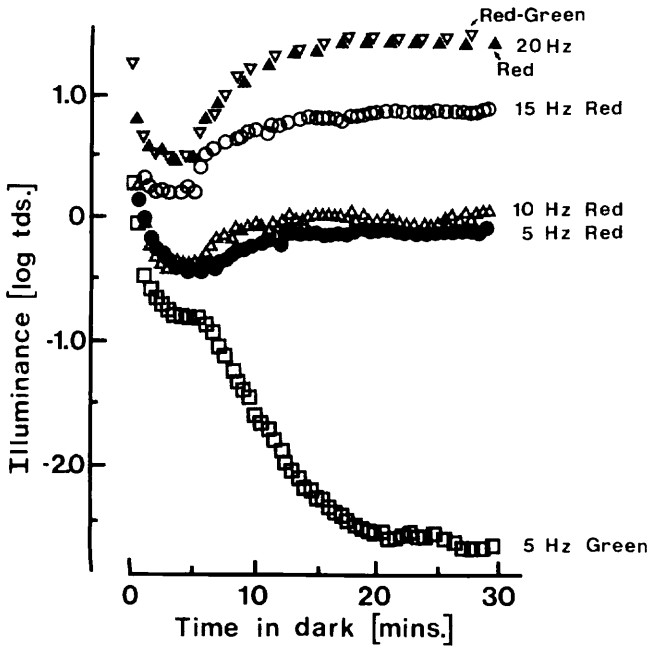

FIG 59–1.
Illuminance of a 2-degree, 20-minute sinusoidally flickered test stimulus presented 7 degrees parafoveally that produces just perceptible flicker as a function of time in the dark. Stimuli were presented in maxwellian view, and flicker was generated by either a red or green light-emitting diode and was either 5, 10, 15, or 20 Hz. Data represented by *inverted open triangles* were obtained with red and green flicker presented in counterphase and matched in scotopic illuminance. (From Goldberg SH, Frumkes TE, Nygaard RW: *Science* 1983; 221:180–182. Used by permission.)

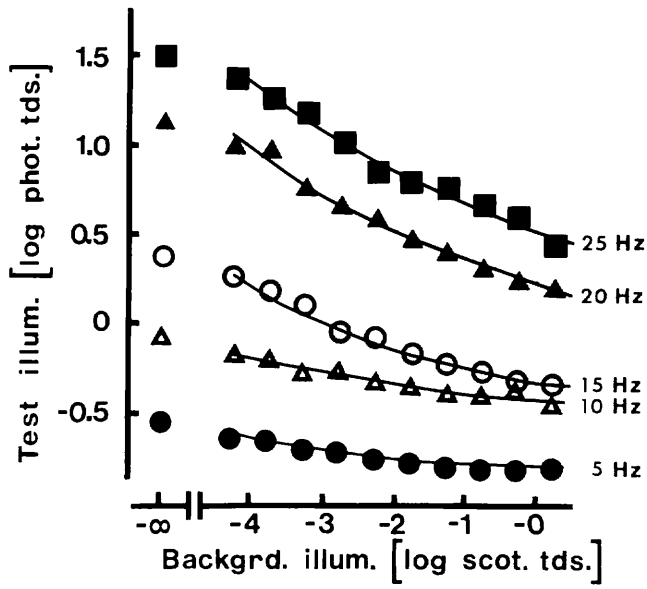

FIG 59–2.
Illuminance of a 2-degree, 20-minute-diameter red flickering test stimulus that produces just perceptible flicker as a function of the illuminance of a 28-degree continuously exposed adapting field of 512-nm wavelength. For the test stimulus, 1 photopic troland is equal to −1.3 log scotopic trolands. Other parameters are as listed in Figure 59–1. (From Goldberg SH, Frumkes TE, Nygaard RW: *Science* 1983; 221:180–182. Used by permission.)

puppy, the limiting irradiance for a 500-nm background is about 1 nW/cm^2, which corresponds to a retinal illuminance of about 1 troland (or under free viewing conditions with an unrestricted pupil, a luminance of about 1 cd/m^2).

Third, the magnitude of SRCI decreases as the size of the flicker probe increases and generally cannot be observed with Ganzfeld stimuli.[4, 6, 22, 40] Pflug and Nelson[40] and Frumkes and Eysteinsson[22] have interpreted this to indicate that SRCI is limited by well-known electrical coupling properties of horizontal cells (e.g., see Lamb[31] and Nelson[38]). SRCI is also largely attributed to the adapted state of rods in retinal areas *adjacent to* rather than *within* the area stimulated by the cone probe.[26, 27] This suggests that SRCI serves as the means for rods to modulate lateral inhibitory influences within the distal retina. As would be expected therefore, rod adaptation exerts as great an influence upon cone-mediated spatial (grating) acuity as on flicker.[15, 37] Flicker is preferred in most studies for its ease in experimentation.

Many other forms of rod-cone interaction are known in addition to SRCI, three of which are noteworthy. First, cone adaptation exerts an influence upon rod-mediated flicker.[25] This phenomenon has not been studied by other psychophysicists, but a very similar effect has been described in the cat retina by electrophysiological procedures.[39, 41] When using ERG procedures, this "reverse effect" may have considerable clinical utility. Second, rod and cone signals summate together: depending upon their relative phase, the signals will either add together to produce a larger sensation or cancel one another out.[16, 35, 46] Third, dark-adapted rods also exert an inhibitory effect upon a specific (correct color detection) threshold.[32] Although much less is known about these other three types of rod-cone interaction, it is quite clear that they are all distinct from each other and from SRCI.[5, 16, 25]

CLINICAL PERSPECTIVE

In most psychophysical and clinical studies of SRCI, the observer adjusts the intensity of a cone-stimulating probe until flicker is just perceived. The

probe is flickered at a fixed frequency (usually between 15 and 25 Hz) and size (between 1 and 2.5 degrees). The magnitude of SRCI is assessed by determining the amount that cone flicker sensitivity is influenced by selective rod adaptation. Although SRCI can be seen with flicker probes placed at virtually any retinal position including the fovea,[4, 14, 16] most investigators prefer to systematically vary rod adaptation and study at most a few retinal positions (e.g., Figs 59–1 and 59–2). In contrast, Alexander and Fishman[1–3] prefer to study only two levels of adaptation but to systematically vary retinal position, as shown in Figure 59–3. I stress this methodological difference at the outset because their conclusions often differ strikingly from those reported by other groups, thus suggesting that sweeping generalizations may be unwarranted.

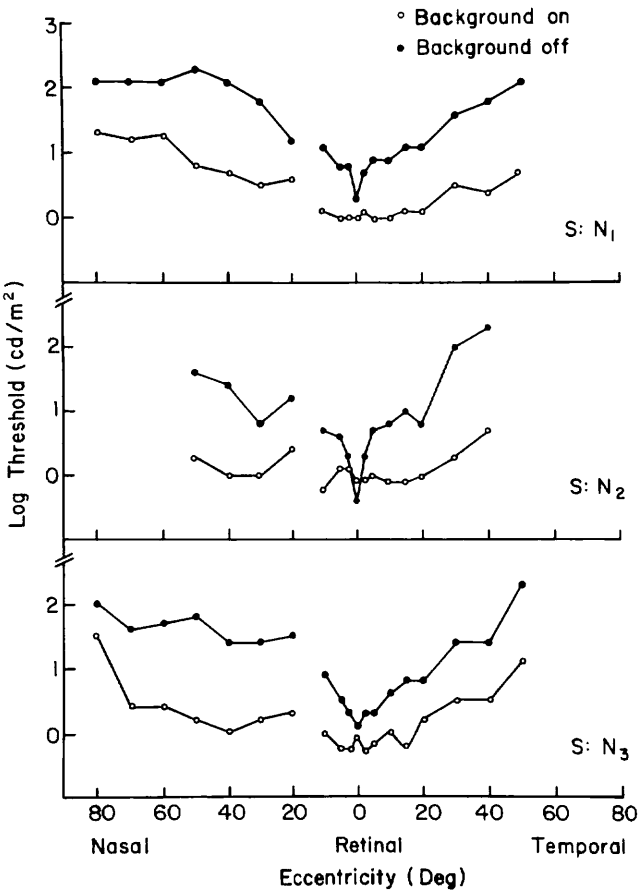

FIG 59–3.
Luminance of a 1-degree, 44-minute-diameter square-wave flickering test probe of 25 Hz that was just perceived as flickering as a function of position on the retina. The stimuli were presented by means of a modified Tübinger perimeter and were presented in the dark *(closed circles)* or against a Ganzfeld background of 0.5 log cd/m^2. Results are from three observers. (From Alexander KR, Fishman GA: *Br J Ophthalmol* 1984; 60:303–309. Used by permission.)

NIGHT BLINDNESS

SRCI has been studied in a variety of night blindness conditions. Arden and his colleagues have reported three types of abnormalities in SRCI that are associated with retinitis pigmentosa (RP). First, SRCI is sometimes lacking or considerably reduced in retinal areas in which rod vision is absent[10]; this was confirmed by Alexander and Fishman.[3] Second, in some patients with dominantly inherited RP, the amount of SRCI was carefully probed on both sides of the "cliff" separating areas of the retina where rods were clearly affected from areas where they were functioning more normally. Obviously, SRCI is missing in the affected retinal areas, but this deficit extended several degrees into "unaffected" areas.[11] Such a finding would be anticipated from a horizontal cell lateral inhibitory model. Third, in some patients in which rod dark adaptation measured by usual psychophysical threshold or fundus reflectometry procedures is slower than normal, the growth of rod inhibition upon cones nevertheless proceeds at a normal rate.[10] A similar dissociation between the time course of rod threshold changes and the growth of inhibition of cones during dark adaptation has been seen also in patients with fundus flavimaculatus.[42, 45] In normals, the antiphosphodiesterase theophylline specifically influences the time course of inhibition upon cones during rod adaptation while having little influence upon rod threshold per se.[30] Since cyclic nucleotides play so critical a role in rod phototransduction, this suggests that in patients with slowed dark adaptation there is some dissociation between photopigment bleaching and the release of neurotransmitter in the dark.

A number of studies have investigated patients with stationary night blindness. This condition is characterized by normal rod rhodopsin content and absent or considerably reduced rod sensitivity; sometimes the ERG has a fairly normal rod a-wave but a considerably reduced or absent rod b-wave. Two groups of investigators have found SRCI to be absent in the six patients they examined.[8, 10, 28, 43] On the other hand, Alexander and Fishman[3, 5] (also personal communication) have found normal SRCI in the three patients they examined. Although there remains the possibility that different groups are describing different diseases with similar symptoms, it is probable that these conflicting findings may reflect

some unresolved methodological difficulty. Indeed, a third possible change in SRCI that is associated with this condition has recently been suggested by ERG procedures.[36]

In a much different vein, Arden and Hogg[9] studied three individuals who appeared absolutely normal after even the most intense traditional clinical testing but who all complained of night vision difficulties: all refused to drive an automobile at night. In all three, the change in cone-mediated flicker sensitivity occurring during rod-dark adaptation was >2.5 $\log_{10}$ units as opposed to about 1 log unit in normals. Recall that SRCI exerts as big an influence upon cone-mediated *spatial* acuity as upon flicker.[37] Apparently, too much rod inhibition upon cone pathways is a "new" cause for night blindness.

DISORDERS OF COLOR VISION

SRCI has been studied in males with common X-linked forms of dichromacy, namely, deuteranopes and protanopes (respectively lacking normal green and red cones). SRCI is apparently normal in the two deuteranopes carefully investigated but is totally lacking in the four protanopes carefully investigated.[13, 22, 26] Although these results have yet to be fully published, several results from the two protanopes investigated by the author prove particularly intriguing. Because inhibition upon cones is lacking, the flicker sensitivity of these individuals in the dark was considerably superior to normal (i.e., the sensitivity level of normals in the presence of an optimal rod-adapting field). One of these men was additionally studied using grating acuity procedures: rod suppression of cone grating acuity is lacking, and hence, his spatial vision is similarly supernormal in the dark. The other protanope studied by the author showed another form of rod-cone interaction involving the use of Stiles' two-color increment threshold procedure.[12, 23] But Alexander and Fishman question the generality of these findings. That is, although they failed to find SRCI in two "extremely protanomalous" individuals,[1] they have since found a normal pattern for SRCI in two protanopes (personal communication). More recently, they suggest that SRCI has little to do with the rod influence upon color perception.[5]

X-LINKED INHERITED CONDITIONS

SRCI is lacking in males with a number of X-linked conditions including protanopia and RP (see above). Although SRCI reflects distal retinal function, Arden and Hogg[8, 10] also find it to be missing in individuals with X-linked retinoschisis, a result again disputed by Alexander and Fishman[3] (also personal communication). More recently, there have been several studies in female obligatory carriers who lack the phenotypical expression of this disease. Arden et al.[7] fail to find SRCI in such women. Arden (personal communication) now has some evidence that SRCI might be similarly absent in carriers of X-linked RP. SRCI is also lacking in individuals with choroideremia and reduced in others who are carriers for this condition.[48]

NEWER DEVELOPMENTS

It is probable that SRCI has value for assessing visual functioning for a wide variety of other disease conditions. Lorenz and Zrenner[33] have associated a number of the complaints of myopes to a reduction in rod inhibition upon cones! The use of SRCI for assessing function in more general conditions such as diabetic retinopathy is still unexplored.

The value of SRCI as a test of visual functioning can be vastly improved. Zrenner and his associates[42, 45, 48] have found alterations in SRCI to be associated with alterations in color vision and particularly the phenomenon of transient tritanopia; Arden also has associated changes in SRCI with changes in color vision. This author can foresee several developments in the near future that will greatly expand the clinical usefulness of SRCI. First, SRCI should be more clearly related to horizontal cell functioning and lateral inhibition. Other than the *Werblin-Westheimer* procedure developed by Enoch,[17] SRCI is probably the only known measure of lateral inhibitory effects in humans that is specifically attributable to the distal retina. Second, SRCI testing should be specifically associated with other types of rod-cone interaction. For example, Denny et al.[16] have developed procedures for testing both a summation of rods and cones as well as SRCI in a single-sitting time period and show that the underlying mechanism must differ considerably. Their procedure should be of great value for studying individuals (RP or fundus flavimaculatus patients) in which the time course of rod threshold recovery and the growth of rod inhibition during dark adaptation are dissociated. If the claim by Alexander et al.[5] for dissociation between SRCI and rod inhibition of color perception is replicated, this too should be of clinical value. Finally, it now seems probable, based upon neurophysiological

findings in lower species,[22, 44, 47] that SRCI possibly reflects a number of distinct mechanisms. If these can be teased apart by simple stimulus manipulation, their value for clinical investigation will be greatly enhanced.

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