an identical manner to that of the ipsilateral sciotic pool and reached a peak at the same time, one day after the nerve lesion. Furthermore, because we prelabelled the motoneurones we were able to demonstrate a small but clear decline in the number of surviving contralateral sciotic motoneurones during the early postoperative period, which could not be established with the labelling methods used previously.

Like Kolzenburg et al., we have considered both peripheral and central mechanisms to explain contralateral motoneurone losses. Together, these observations suggest a central neuronal mechanism is most likely. In view of the fact that our studies are carried out in neonates, two particular points might be pertinent. First, neuronal connections crossing the midline are thought to be more substantial in immature spinal cord.

Second, there is evidence that increased activation alone can cause degeneration of immature motoneurones. Thus, we suggested that death of contralateral motoneurones might be attributable to increased activation through a pathway crossing the midline.

The use of apoptotic techniques has also allowed us to observe the effect of a nerve lesion on spinal interneurones. Previously, we established that these cells underwent a discreet wave of naturally occurring cell death immediately after birth, but following sciotic nerve injury, interneurone death was significantly higher than the background level both ipsilaterally and contralaterally. The increase on both sides occurred simultaneously but was delayed until three days after the peak of motoneurone death. Interneurone death was more obvious in the dorsal horns, suggesting that it was either consequent on altered sensory input, perhaps through increased activation, or secondary to loss of dorsal-root-ganglion cells.

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References

Letters to the Editor

Rod pathways: the importance of seeing nothing

Lindsay T. Sharpe and Andrew Stockman

Anatomical and physiological studies of the mammalian retina have revealed two primary pathways available for the transmission of rod signals to the ganglion cells: one via ON rod bipolars, amacrines II, and ON and OFF cone bipolars, which is exclusively designed for the transmission of single-photon absorption events; and a second via rod–cone gap junctions, and ON and OFF cone bipolars, which is designed for the transmission of multiple photon-absorption events at higher light levels. Psychophysical and electroretinographic (ERG) studies in normal observers and in two rare types of observer, who are devoid of either rod or cone function, suggest an analogous duality in the human visual system, the clearest signature of which is a loss of flicker visibility and ERG amplitude at frequencies near 15 Hz that results from destructive interference between sensitive ‘slow’ and insensitive ‘fast’ rod signals. The slow rod signal is most probably derived from the ON rod bipolar pathway and the fast signal from the rod–cone gap junction and cone pathways. Evidence has emerged recently for a third, insensitive rod pathway between rods and OFF cone bipolars, but it has so far only been observed clearly in rodents.


The mammalian retina contains two distinct types of photoreceptor: the rods and cones (see Fig. 1). Both hyperpolarize in response to light, reducing the synaptic release of their transmitter, glutamate. Cones subserve daylight or photopic vision, when photons are abundant. Together, with a specifically evolved neural circuitry, they are responsible for the perception of fine temporal and spatial detail, and for colour vision. In contrast, rods mediate starlight–twilight or scotopic vision, when photons are few. Their design is optimized for the reliable transduction of single-photon absorptions. Aside from specialized bipolar cells and amacrines (see below), however, the retinal circuitry for rod signals appears to be superimposed upon preexisting cone circuitry in ways that afford multiple opportunities for signal transmission.

In this article, evidence for the routing of rod signals over more than one pathway is reviewed from: (1) non-human anatomy and physiology (see earlier reviews in Refs 1,5); and (2) human electrophysiology and psychophysics. The amalgamation of information from these disciplines yields insights into the behavioral and functional significance of having multiple rod pathways.

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LETTER TO THE EDITOR

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Anatomical and physiological evidence for multiple rod pathways

ON rod bipolar and All amacrine pathway

The first route to be identified was the rod ON bipolar and All amacrine pathway. Unlike cold-blooded vertebrate rods, mammalian rods are thought to synapse with a single type of bipolar cell, the so-called ON type, which depolarizes following light stimulation (but see below). The synapse is at the apex of the deeply clefted rod spherule (see Fig. 1).

One synaptic ribbon, which is densely filled with vesicles containing glutamate, interacts with two or more invaginating rod ON bipolar dendrites that bear mainly the high-affinity sixth-subtype metabotropic glutamate receptor (mGluR6)9–12, but that also contain some ionotropic glutamate receptor (iGluR) subunits13. The rod ON bipolar, in turn, contacts the amacrine AII cell at a sign-conserving glutamate synapse3,14–17 (a synapse at which neurotransmitter release results in hyperpolarization of the postsynaptic membrane). Signals from the amacrine cell then infiltrate the main cone circuitry (see Box 1) by exciting ON (depolarizing) cone bipolar cells through sign-conserving electrical gap junctions and inhibiting OFF (hyperpolarizing) cone bipolar cells through glycinergic synapses (see Fig. 1)3,17–20. Thereafter, the signal separation is maintained: ON bipolars excite ON ganglion cells and OFF bipolars excite OFF ganglion cells.

Rod–cone gap-junction pathway

A second pathway infiltrates the ON and OFF cone bipolar circuitry at the earliest possible stage. Telodendria projecting from the sides and bases of neighbouring cone pedicles make minute gap-junction contacts with rod spherules (see Fig. 1), which allow electrical synaptic transmission21–25. Between three and five gap junctions occur on a single rod spherule with the majority originating from either red (long-wavelength-sensitive) or green (middle-wavelength-sensitive) cones26. Through the gap junctions, rod signals have access to ON and OFF cone bipolars and thence to ON and OFF ganglion5,23,24,27. The viability of the rod–cone gap junctions as a means of transmitting rod signals has been established in the cat by Nelson23, and in the macaque monkey by Schneeweis and Schnapf28, both of whom demonstrated the presence of rod signals in cones. In addition, the cell bodies of primate H1 horizontal cells have been shown to receive rod input29,30, which is likely to arrive via the rod–cone gap junctions, cones and H1 dendrites. Although the H1 axonal tree contacts rods, the long thin axon isolates electrotonically the axonal tree from the cell body and dendritic tree that only contacts cones31,32.
An OFF bipolar pathway?

Evidence for a third pathway, involving a direct OFF bipolar pathway, is provided by the following observations. In rats, OFF bipolar cells form the major substrate of the parvocellular pathway. In contrast, OFF bipolar cells are present in several species, including between 5 and 10 cones in central to mid-peripheral retina. They contact rods with the same sign (D.J. Calkins, PhD Thesis, University of Pennsylvania, 1994). They are also present in gray squirrel and black bear retinae. They are found in cat or macaque monkey retina. They contact rods and spherules and putative OFF bipolar cells have not been found in cat or macaque monkey retina.

References

Box 1. Cone pathways

At least nine types of ON and OFF bipolar cell contact the cone pedicle. Their response polarity is determined by the nature of their receptors. In ON bipolar cells, metabotropic glutamate receptors link glutamate to the closure of cation channels; whereas in OFF bipolar cells, ionotropic glutamate receptors link glutamate to Na⁺ influx. The ON bipolar axons terminate in the sublamina b of the inner plexiform layer (IPL), synapsing with ON-centre ganglion cells, whereas the OFF bipolar axons terminate in sublamina a, synapsing with OFF-centre ganglion cells.

Midget bipolar contacts exclusively, at least out to retinal eccentricities of 50° of visual angle, single M- or L-cone pedicles. They are either of the invaginating (ON bipolar) or the semi-invaginating (OFF bipolar) type. In turn, they connect to single midget ganglion cells of the same sign (D.J. Calkins, PhD Thesis, University of Pennsylvania, 1994), the projections of which, to the lateral geniculate nucleus, form the major substrate of the parvocellular pathway. Differences in bipolar cell pool information from several cones, contacting between 5 and 10 cones in central to mid-peripheral retina. They are thought to connect to the parasol ganglion cells with which they form the main substrate of the early magnocellular pathway. There are at least six variances, which are identified according to whether they have predominantly invaginating or basa contacts with cone pedicles and according to whether they synapse in sublamina a or b of the IPL. Types DB1, DB2 and DB3, believed to be OFF types, have basa contacts and terminate in sublamina a of the IPL (Refs a,j,n); types DB4, DB6 and DB8, believed to be ON types, terminate in sublamina b (Refs a,j,m) and have predominantly ‘invaginating’ contacts (though types DB8 and DB6 have significant numbers of basal contacts).

In primates, the All amacrine cells of the primary rod circuit probably contact both midget and the diffuse bipolar cells, and so provide (along with the rod-cone gap junctions) rod input to both the parvocellular and magnocellular pathways. In general, however, rod signals appear to be more prevalent in magnocellular than in parvocellular projecting cells.

References

Box 2. Receptor antagonists

Chemical antagonists can be used to reveal the flow of photoreceptor signal transmission in retinal networks by blocking transmission at a subset of synapses. The glutamate analog, AFB, acts selectively on metabotropic glutamate receptors, blocking transmission from photoceptors to ON bipolar cells; but not to the OFF bipolar cells. Strychnine interferes with the glycinergic synapse of the All amacrine cell, blocking transmission to the cone OFF bipolar cell.

References
Fig. 2. Rod self-annihilations in human rod flicker data. (A) 15 Hz rod-flicker detectability data for a normal observer plotted as a function of background retinal luminance (log scot. td). The filled circles represent a rod-flicker threshold versus intensity (TVI) function (that is, they represent the lowest intensity at which rod flicker is just detectable plotted as a function of background intensity). The function is clearly double-branched. The upright and inverted triangles on the left of the TVI function represent, respectively, the lower and upper limits of the region within which 15 Hz flicker could not be seen (shaded gray). The disappearance of flicker occurs well below the cone-flicker thresholds measured before the rods have recovered from an intense bleaching light (open circles). The disappearance is also found in a rod monochromat, who lacks functioning cones. (B) Illustration of how 15 Hz self-annihilation might occur. A single flickering 15 Hz red stimulus (a) produces a fast signal (b) and a slow signal (c) that is delayed by a half cycle (33.3 ms) relative to the fast one. When recombined, the slow and fast signals destructively interfere (d) to produce a steady signal with no visible flicker. (C) Rod-cone phase lags measured as a function of scotopic intensity at flicker frequencies of 8 Hz (filled circles) and 15 Hz (open squares) in the same normal observer as in (A). The region of invisible 15 Hz flicker is shown in gray. Data in (A) and (C) are replotted from Ref. 50.

Evidence from human psychophysics and electrophysiology for multiple rod pathways

Are the multiple rod pathways demonstrated in mouse, rat, cat, rabbit and macaque retinas also found in the human visual system? And, if so, what is the behavioral and functional significance of each of them? The answer to the second question is important because some ‘pathways’ could be involved in modulatory functions, such as sensitivity regulation, rather than the transmission of crucial details of the visual world.

First evidence

The earliest evidence for two rod pathways pre-dates the physiological and anatomical evidence. It came from psychophysical measurements of temporal resolution made more than 50 years ago in a rare, totally colour-blind human observer, a rod monochromat who lacked cone vision. The measurements revealed two distinct stages in the function that relates critical flicker frequency (CFF) to intensity, separated by an inflection near 0 log scot. td. Crucially, alongside the break in the curve is a region within which 15 Hz flicker is invisible. Thus, as the intensity of the flickering target is increased, the flicker becomes visible, but then disappears before reappearing again at higher intensities.

The CFF of 15 Hz flicker is consistent with destructive interference between a fast rod signal and a slow one that is delayed by approximately 33.3 ms (that is, by half the 15 Hz period). As illustrated in Fig. 2B, a relative delay of 33.3 ms means that, when recombined, the two signals are in opposite phase and cancel each other. Measurements of the perceptual delay between rod and cone signals at intensities just above and just below the intensity region in which the CFF is invisible confirm that these perceptual phenomena arise from destructive interference between two rod signals with different latencies. Results of such measurements are shown as a function of intensity in Fig. 2C for frequencies of 8 Hz and 15 Hz. The disappearance of flicker is associated with an abrupt change in phase delay from approximately 180° to 90° for 8 Hz flicker and from 360° to 180° for 15 Hz flicker, which are consistent with a reduction in time delay of approximately 33.3 ms (Ref. 50).

Electrophysiological evidence from normals

Further electrophysiological evidence for multiple rod signals that are both frequency- and intensity-dependent can be found in the human electroretinogram or ERG (Ref. 49). Figure 3 shows ERG responses to 15 Hz Ganzfeld (full-field) flicker in the normal observer. With increasing flicker intensity, the ERG amplitude grows slightly, but then falls to a minimum at an intensity near a temporal frequency of 15 Hz and an intensity of 0 log scot. td. Figure 2A shows a typical example in the form of rod-flicker threshold data measured in a normal observer under conditions chosen to favour rod-flicker detection. Conspicuously, the rod-determined part of the flicker threshold versus intensity (TVI) curve, like the CFF function, exhibits two stages, with a break occurring near a background intensity of 0 log scot. td. Crucially, alongside the break in the curve is a region within which 15 Hz flicker is invisible. The disappearance of 15 Hz flicker is consistent with destructive interference between a fast rod signal and a slow one that is delayed by approximately 33.3 ms (that is, by half the 15 Hz period). As illustrated in Fig. 2B, a relative delay of 33.3 ms means that, when recombined, the two signals are in opposite phase and cancel each other. Measurements of the perceptual delay between rod and cone signals at intensities just above and just below the intensity region in which the flicker is invisible confirm that these perceptual phenomena arise from destructive interference between two rod signals with different latencies. Results of such measurements are shown as a function of intensity in Fig. 2C for frequencies of 8 Hz and 15 Hz. The disappearance of flicker is associated with an abrupt change in phase delay from approximately 180° to 90° for 8 Hz flicker and from 360° to 180° for 15 Hz flicker, which are consistent with a reduction in time delay of approximately 33.3 ms (Ref. 50).

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intensity corresponding to the perceptual disappearance of the flicker (0.02–0.13 log$_{10}$ scot. td) before growing more. Consistent with destructive interference being the cause of the flicker loss, the phase of the response abruptly reverses by a half cycle as the minimum is crossed.

Special cases: evidence from human observers devoid of cone or rod function

A strategy in psychophysics that is often revealing is the use of observers with special visual deficits. Two types of observers have been used to study the underlying physiology and anatomy of the rod pathways: rod monochromats and individuals with congenital stationary night blindness (CSNB).

**Rod monochromat**

The classical signatures of the two rod signals, including the dual CFF and TVI functions, the flicker disappearance, and the minimum and phase reversal in the ERG, are all also found in a rod monochromat whose vision has consistently been demonstrated to lack functioning cones. Molecular-genetic analysis has established that he has homologous mis-sense mutations in a gene (CNGA3) on chromosome 2 that encodes the α-subunit of the GOMP-gated cation channel in the cone photoreceptor, the presence of which renders them inexcitable.

![Figure 4A,B highlights the similarity of the ERG estimates of phase delay between the slow and fast rod signals in the rod monochromat and normal subject.](image)

**Fig. 3. Rod self-cancellation in human electrophysiological data.** Cancelled electroretinogram (ERG) recordings at 15 Hz for the normal observer. The time-averaged flicker intensity increases upwards in steps of approximately 0.22 log$_{10}$ unit ranging from −1.56 to 1.25 log$_{10}$ scotopic troland (scot. td). The mean intensity in log$_{10}$ scot. td is noted to the right of each record. The vertical broken lines highlight how the phase abruptly changes by 180° between the flicker intensities immediately above and below the region (~0.15 log$_{10}$) in which rod flicker is invisible. The positions of the ERG responses with respect to the y-axis are arbitrary. Data replotted from Ref. 52.

![Graph showing rod self-cancellation](image)

Conceivably, this sluggish, insensitive signal could be the one being conveyed by the rod-cone gap junctions, but it is not the same fast rod signal that cancels the slow rod signal psychophysically and electrophysiologically at 15 Hz. It should be noted, however, that the results from observers with congenital visual deficits might be unrepresentative. Through plasticity, those deficits could lead to the development or prominence of retinal connections that are normally missing or unimportant.

**Bringing together the human and non-human evidence**

The psychophysical evidence clearly indicates at least a duality of rod vision. A slow, sensitive rod signal is superceded by a fast, insensitive one as the light increases from scotopic to mesopic levels. The remarkable consistency of the electrophysiological and psychophysical data suggests that the two rod signals are retinal in origin. Support for a retinal location also comes from one of the few physiological studies measured under relevant conditions that uses flicker: in the cat, Nelson et al. reported phase delays between ganglion and AII amacrine cells at mesopic levels (levels at which both rods and cones are active) that were comparable to those found in humans. So how do the slow and fast rod-flicker signals correspond to the anatomically described retinal rod pathways? (For alternative possibilities and the problems associated with them, see Box 3.)

The sensitive, slow rod signal is most likely to be transmitted by the primary ON rod pathway routed by way of rod bipolars and AII amacrine cells. Several lines of reasoning support the assignment. First, the pathway...
is well designed for high sensitivity. In cat central retina, signals from ~1500 rods converge onto a single ganglion cell, principally at the stages from rods to rod bipolar cells and from rod bipolar to All amacrine cells. With amplification at each stage, threshold nonlinearities to reduce transmitted noise at the rod to rod-bipolar synapse and noise averaging at the All amacrine cell, the circuit is exquisitely designed to enable the transmission of single photon events. Second, the sensitive ON and OFF rod responses are eliminated at ganglion cells by blocking the ON rod bipolar cells with APB in cats and mice (see Box 2). Third, strychnine blocks the sensitive OFF rod response (see Box 2). Fourth, All amacrine cells are active at scotopic but not high mesopic levels. Fifth, the scotopic threshold response in cat, which is likely to be generated by rod-driven amacrine cells, has a similar response-intensity function (linear growth with log intensity, followed by saturation) to that of the slow rod signal in the human ERG, and both are very different from the function for the fast rod signal (Figure 3A). Sixth, the fast rod signal (linear growth with linear intensity) is less certain. What does seem clear, given that Nelson et al. observed a clear rod response at mesopic levels in cat ganglion cells but none in All cells, is that the fast signal bypasses the All amacrine cells. The most-obvious route by which this can be effected is via rod-cone gap junctions. Evidence from cat and monkey shows that signal transmission by way of the rod-cone gap junction is indeed stable, and calculations suggest that the gap-junction signal should become significant at the appropriate luminance levels.

Although the results obtained in the rod monochromat and CSNB observers of the complete Schubert-Bornschein type cast some doubts, most of the evidence supports the gap-junction model of the fast pathway, in which a multi-photon signal is ‘piggybacked’ onto the cone bipolar circuit. The fast signal might survive in rod monochromats because the few non-functioning cones that remain (see above) can provide enough rod-cone gap junctions to support a fast signal. In addition, CSNB patients of the complete Schubert-Bornschein type might fail to receive the fast rod signals because of possible post-receptoral abnormalities in both their rod and their cone bipolar pathways (see, for example, Refs 78–81). The finding of a transient as well as a sustained rod response in cones and in the cell bodies of the H1 cells suggests that rod-cone gap junctions in the normal retina can transmit high as well as low temporal frequencies.

The phase data in Fig. 4A,B imply that the predominately fast rod signal at lower frequencies must have the same sign as the slow signal, as they tend towards 0° at 0 Hz. However, as noted by Stockman et al., at frequencies above 10 Hz the data, particularly those for the rod monochromat, might also be consistent with the fast rod signal being opposite in sign to the slow signal, as the higher frequency data extrapolate to ~180° at 0 Hz. A speculative conclusion is that the ‘fast’ rod signal is actually composed of two signals: (1) a sluggish ON signal transmitted by rod-cone gap junctions that predominates at low frequencies, which can be seen most clearly in the CSNB data; and (2) a faster OFF signal transmitted by rod to OFF cone bipolar connections that predominates at frequencies above 10 Hz, which can be seen most clearly in the rod monochromat data. Overall, however, the simpler model seems more plausible.

Concluding remarks: multiple pathways

It might be unrealistic to impose a simple two- or even three-pathway scheme on the maze of largely unexplored post-receptoral circuitry in the mammalian retina. The rod signals that we identify as ‘slow’ and ‘fast’ might derive from several sources. The fast rod
Box 3. Multiple rod signals: alternative explanations

The retina can distinguish between two types of rod signals, which are high sensitivity or low sensitivity, depending on the intensity of the stimulus. High sensitivity signals are carried by the rod bipolar cells, which are sensitive to dim light conditions. On the other hand, low sensitivity signals are carried by the rod-cone bipolar cells, which are sensitive to bright light conditions.

References

HE TERM ‘CHEMOKINE’ was originally adopted to describe a family of chemotactic cytokines that were, on the whole, smaller than the inflammatory cytokines and exhibited a characteristic N-terminal cysteine motif (see below). In general, chemokines are small proteins (8 to 10 kD) that induce chemotaxis, tissue extravasation and functional modulation of a wide variety of leukocytes during inflammation. In view of these properties, intense research efforts have focused recently on the possible involvement of chemokines and their receptors as targets for therapeutic intervention in CNS disease.

The past decade has witnessed the remarkable ascendance of chemokines as pivotal regulatory molecules in cellular communication and trafficking. Evidence increasingly implicates chemokines and chemokine receptors as plurifunctional molecules that have a significant impact on the CNS. As plurifunctional mediators in diverse states, chemokines and chemokine receptors have an important role in cellular communication and trafficking. Evidence increasingly implicates chemokines and chemokine receptors as targets for therapeutic intervention in CNS disease might now have to be considered in the context of the broader physiological functions of these molecules.