Cyclic metabolism of photoreceptor cells

This issue of Investigative Ophthalmology & Visual Science contains three papers dealing with the cyclic nature of photoreceptor cell metabolism. This field of investigation represents one of the most active areas of vision research today. The speed and range of studies on photoreceptors and their supportive tissue, the pigment epithelium, have accelerated to the degree that more new information on the control mechanisms of outer segment turnover has been obtained within the last 2 years than had formerly been obtained in a decade.

Any chronology of this line of investigation must begin with a reference to the early ultrastructural studies of the human pigment epithelium by Bairati and Orzalesi. These authors were the first to interpret correctly the lamellar inclusion bodies within this tissue, now termed phagosomes, as having originally been a part of the photoreceptor outer segments. They further suggested that the detachment and phagocytosis of this material from the outer segment tip should be balanced by the addition of newly formed membrane material to the outer segment base. This set the stage for the classic autoradiographic studies of Young and Droz, which firmly established that the outer segment membranes of rod photoreceptors are renewed throughout life. When animals were injected with radioactive amino acids to label newly synthesized protein, the first site of incorporation was within the photoreceptor inner segment as had been observed by Droz earlier. Much of this newly synthesized protein was then transported to the outer segment base where it was used to form a band of radioactive outer segment membrane discs. As this process of membrane addition continued, the radioactive band was displaced along the length of the outer segment to the tip where it was shed as a packet of membrane discs. These membrane fragments were then phagocytized and degraded by the pigment epithelium. The experiments of Hall et al. further demonstrated that much of the new membrane protein was the rod visual pigment rhodopsin. This pattern of rod outer segment renewal has been observed in every vertebrate examined.

Throughout these autoradiographic studies, cone outer segments were observed to become diffusely labeled, but a discrete band of labeled discs was never formed. This led Young to suggest that cone outer segments were renewed by the replacement of individual molecules throughout the outer segment rather than by the rod system of membrane assembly at the base and loss of membrane packets from the tip. However, the morphological studies of cone photoreceptors in the squirrel retina by Anderson, Fisher, and Steinberg and in the human retina by Steinberg, Wood, and Hogan
left little doubt that cones shed packets of outer segment membranes from their tips in a manner analogous to rod shedding. It now appears that the structural differences between rod and cone outer segments are sufficient to account for the contrasting renewal patterns seen with autoradiography. The molecular mechanisms of renewal and shedding in rods and cones may be very similar.

Perhaps the most important observation responsible for tying the earlier studies together and initiating much of the recent work was LaVail's discovery of the cyclic nature of rod shedding. In rats housed under cyclic lighting, rod outer segments shed shortly after the onset of light. Cyclic shedding of rods has been confirmed and extended in a variety of animals. Young recently found cone shedding in nonmammals to be cyclic, occurring shortly after the beginning of the dark cycle, and Bunt confirms the timing of rod and cone shedding in the rabbit as occurring at the beginning of the light and dark cycle respectively.

Recent studies on the frog retina have shown that alterations in the normal photo-period result in significant changes in the shedding response. Constant light virtually eliminates rod shedding, although disc addition continues and thus the outer segments elongate. In constant darkness, rod shedding is reduced but appears to occur in a circadian manner, and again, with renewal continuing, the outer segments elongate. These studies stress that a normal photo-period is essential to maintain photoreceptor metabolism such that disc addition is balanced by disc loss. It is this delicate balance between renewal and shedding which is responsible for maintaining a constant outer segment length throughout adult life.

Are the events initiated by transitions from dark to light and light to dark, which stimulate rod and cone shedding respectively, expressed entirely within the retina, or do they involve control or mediation by higher neural centers? Ionic fluxes and/or changes in cyclic-nucleotide concentrations related to transduction could be involved in shedding. However, the circadian nature of rod shedding and its dependence on the photoperiod suggest that higher centers may be involved. For example, daily rhythms in serotonin-melatonin metabolism are known to control a variety of cellular activities (e.g., reproductive, locomotor). Close parallels exist between changes in the pineal output and blood levels of melatonin and the times of rod and cone shedding. However, pinealectomy does not appear to reduce shedding in frog rods, so that if this hormone does affect shedding, it is possible that the control process is entirely intraocular because, at least in amphibians, the eye contains the enzymes necessary for converting serotonin to melatonin. Alternatively, products of the pituitary or other neuroendocrine effectors, notably those which affect calcium or cyclic-nucleotide metabolism, are possible candidates for a role in the shedding process.

Evidence is also accumulating which indicates that membrane addition to rods is also cyclic and does not occur at a constant rate. When measured by radioactive band displacement, most of the daily increment occurs during the light phase of the diurnal cycle, and during the same interval, the number of newly formed discs (open discs) at the base of the rod outer segment increases threefold. It is possible that this cyclic pattern of outer segment assembly results from a cyclic pattern in transcription and/or translation. Certainly one of the major goals of vision scientists working in this area is a complete description of the molecular events which regulate and initiate these cyclic phenomena.

The maintenance of normal, healthy outer segments is critical to vision, and the devastating abnormalities which occur at the outer segment/pigment epithelium interface are among the least understood and difficult to manage clinically. It seems reasonable to suggest that a breakdown in the delicate balance between renewal and shedding might be responsible for the outer segment degeneration and blindness manifest in some types of retinitis pigmentosa. Hopefully, the recent rapid rate of advances in our under-
standing of this area will continue, and further information on both control mechanisms of renewal and shedding and their role in retinal pathogenesis will be forthcoming. A firm understanding of the cyclic nature of photoreceptor metabolism, outer segment renewal, and rod and cone shedding would be helpful in formulating more effective treatment for one of man's most feared diseases.

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REFERENCES