Exp. Eye Res. (1985), **41**, 497–507

The Diurnal Susceptibility of Rat Retinal Photoreceptors to Light-induced Damage

THANE E. DUNCAN AND W. KEITH O'STEEN

Department of Anatomy, Bowman Gray School of Medicine, Wake Forest University Medical Center, Winston-Salem, North Carolina 27103, U.S.A.

(*Received 9 December 1984 and accepted 6 June 1985, New York*)

Exposure of albino rats to high intensity light results in rapid, graded loss of photoreceptors. The hormonal status and age of an animal at the time of exposure affect the severity of light-induced retinal damage. The adrenal axis and pituitary hormones (prolactin) have been demonstrated previously to affect the degree of cell death in the retina. Because circadian rhythms for adrenal and pituitary secretion have been demonstrated in the rat, a series of experiments was undertaken to determine if a diurnal pattern of retinal susceptibility to light damage exists which might be related to endogenous endocrine rhythms. Male Sprague–Dawley rats were exposed to 4 hr of high intensity fluorescent light for 8 consecutive days during different phases of the 14:10 hr light: dark animal room light cycle. Morphometric analysis performed at the light microscopic level 2 weeks after exposure demonstrated a differential susceptibility to light-induced cell death depending upon the period during the light–dark cycle when animals received their daily light exposure. Neuronal cell death was confined to the outer nuclear layer as previously described. The retinas of animals exposed during the middle of the dark period or during the first 5 hr of the light period were significantly more damaged than the retinas of animals exposed during the last 9 hr of the light period. Control groups for the relative amounts of dark–adaptation between groups suggested that the diurnal susceptibility to light damage was not solely dependent upon the degree of dark adaptation. These results demonstrate a diurnal susceptibility of photoreceptors to light-induced cell death.

Key words: retina; photoreceptors; retinal damage; cell death; diurnal susceptibility; cyclic photoperiod; hormones; light damage.

1. Introduction

The phenomenon of light-induced retinal damage is well documented, and rat retinas (Noell, Themann, Kang and Walker, 1966; O'Steen, 1970), as well as those of rabbits (Lawwill, 1973), pigs (Sisson, Glauser, Glauser, Tasman and Kuwabara, 1970), monkeys (T'so, 1973; Friedman and Kuwabara, 1968) and humans (Radnot, Jabbagy, Heszinger and Lovas, 1969) are known to be damaged irreversibly by exposure to high intensity illumination. When animals are exposed to light, there is a rapid, graded loss of retinal photoreceptors which may be quantified both as a reduction in the amplitude of the electroretinogram (ERG) and as a measurable reduction in the thickness of the outer nuclear layer (ONL), which contains the cell bodies of the photoreceptors. The degree of retinal damage is dependent upon the wavelength, intensity and duration of illumination and the temperature of the animal during exposure (Noell, Walker, Kang and Berman, 1966). A number of mechanisms have been proposed for the effect of light on the retina; however, the mechanism remains as yet undisclosed (Noell, 1980). Interestingly, the age (Ballowitz and Dämmrich, 1972; O'Steen, Anderson, and Shear, 1974) and hormonal status (for review see O'Steen, 1980) of an animal at the time of exposure have been demonstrated repeatedly to affect the severity of light-induced damage. The mechanism and primary effectors are not known, but prolactin (O'Steen and Kraeer, 1977), estrogen (Olafson and O'Steen, 1976), pinealectomy (Rudeen and O'Steen, 1979) and, recently, the

0014–4835/85/040497+11 $03.00/0

adrenal axis (O'Steen and Donnelly, 1982) have been demonstrated to be associated with the phenomenon. Hormones have been demonstrated to affect cell death in many neuronal systems, including the hippocampus (Landfield, Baskin and Pitler 1981) and hypothalamus (Brawer, Schipper and Naftolin, 1980; Gorski, 1971). Documented circadian rhythms of ACTH (Krieger, 1977), and corticosterone (Guillemin, Dear and Liebelt 1959; Kreiger, 1979) exist in the rat.

During early investigations of the relationship between stress and light-induced retinal damage (Duncan, O'Steen and Donnelly, 1982; Duncan, O'Steen, Brodish and Donnelly, 1982), the degree of retinal damage appeared to vary according to the time when animals began a 24-hr continuous light exposure. The question arose as to whether the slight circadian changes in serum hormone levels might account for the differential susceptibility. In order to test this hypothesis, it was necessary to expose animals to shorter pulses of light, since a 24-hr exposure period obviously overlapped all of the 24-hr hormonal rhythms and would not have permitted the distinction of a more from a less susceptible period for light damage. Therefore, a regimen was designed in which animals were exposed to short daily pulses of high-intensity light for 8 consecutive days. This series of experiments was performed to determine if the retina had a diurnal variation in susceptibility to light-induced cell death.

2. Materials and Methods

Male Sprague–Dawley rats (90 days old) were maintained in a cyclic light environment [14:10, light–dark, (L:D); 65 lx], in an animal room adjacent to the laboratory for at least 1 week prior to high intensity light exposure. After the beginning of light exposure, animals were kept in the animal room when not in the exposure chamber. Water and rodent chow (Purina No. 5001) were provided ad libitum. Groups of animals were placed in polycarbonate cages with wire tops and minimal bedding and exposed to 4 hr of light per day for 8 consecutive days during different periods of the light–dark cycle. The light intensities to which the animals were exposed were either 65 lx (animal room light level, ALT) or 2260 lx (HLT) of fluorescent light as measured with a Tektronix J16 digital photometer with the illuminance probe directed toward the light source at animal eye level. The illuminance source had a spectral range of 397–732 nm with a maximum at 590 nm. The exposure chambers were 54 cm square wooden boxes provided with continuous air exchange. Temperature during light exposure was maintained at $30 \pm 1{\cdot}5$ °C.

The experimental animals were divided into eight groups. Group 1 was a home cage control and remained in the animal room (ALT, 65 lx) until autopsy. Group 7 was exposed to ALT for 4 hr day^{-1} during the mid 4 hr of the darkness period. All other groups were exposed to an illuminance (HLT, 2260 lx) greater than that of the animal room for 4 hr day^{-1} at different times of the cyclic photoperiod: group 2, beginning at onset of cyclic light period; group 3, 1 hour after onset; group 4, mid 4 hr; group 5, latter 4 hr; group 6, mid 4 hr of darkness; group 8, exposed to 1 hr of light (ALT, 65 lx) followed by 4 hr of HLT during the mid 5 hr of darkness.

Therefore, all animals which were exposed to HLT received a total of 32 hr in the light chambers.

Eyes were enucleated from over-anaesthetized animals 2 weeks after the exposure period to allow for phagocytic removal of dead and damaged cells from the retina (O'Steen and Donnelly, 1982). Prior to removal, the superior surface of the eyes was marked with an indelible pen for future orientation during sectioning and measurement.

The eyes were fixed in Bouin's solution for 5 hr, dehydrated in an alcohol and xylene series and embedded in Paraplast (Lancer). Tissue blocks were sectioned at 7 μm on the anterior–posterior axis, and central sections of the retina including the optic nerve were stained with Harris' hematoxylin and eosin. Thickness measurements of the entire retina and the outer nuclear layer (ONL) were made on each retina with an ocular micrometer as previously described (O'Steen and Donnelly, 1982). Statistical analyses included an analysis of variance with post-hoc Newman–Keuls multiple range test or the Tukey test for significance between groups within each experiment.

Three experiments with identical protocols were performed (Exps 1, 2 and 3) and additional control groups were added to each subsequent experiment. Because animals exposed during the dark period or at onset of the light period were dark-adapted, additional groups were included which were exposed to high intensity light after receiving either a 1 hr light-adaptation in the animal room (group 3), or a 1 hr timed 65 lx light exposure (group 8). Additional animals remained in the animal room during the course of the experiment to control for retinal changes occurring as a result of normal aging and animal room light exposure (group 1). Group 7 was included to control for the extended light period for animals exposed during their normal dark period.

TABLE I

Experimental groups and the time of light onset for experiments 1, 2 *and* 3

Experiment	Month	Time of light onset	Groups
1	December	0500 hr	1, 2, 4, 5
2	April	0830 hr	1–7
3	September	0600 hr	1–8

The time of onset of the light period was different for each experiment (Table I). However, all exposure periods remained in the identical relationship to the respective light cycle and not to clock time. Figure 1 illustrates the relationship between each of the light exposure periods and the animal room light cycle.

3. Results

In all cases, exposure of male albino rats to 32 hr of high intensity fluorescent light administered 4 hr day^{-1} for 8 consecutive days resulted in significant photoreceptor cell death in the retina as measured by a reduction in ONL thickness (group 1 vs. groups 2–6, $P < 0{\cdot}01$; see Figs. 2, 3, and Table II). Retinal damage was limited to the ONL, and no obvious reduction in the thickness of the inner retinal cell layers was observed, although a quantitative analysis of other layers was not undertaken.

The results obtained from each experiment are presented separately. Statistical analysis was not performed to compare between experiments, due to routinely observed variations in the baseline thicknesses of the ONL between different groups of non-exposed animals (see group 1, experiment 1 vs. 2, Figs 2 and 3). For this reason, a group of rats that were kept in the animal room was included in each experiment to provide a baseline for retinal thickness.

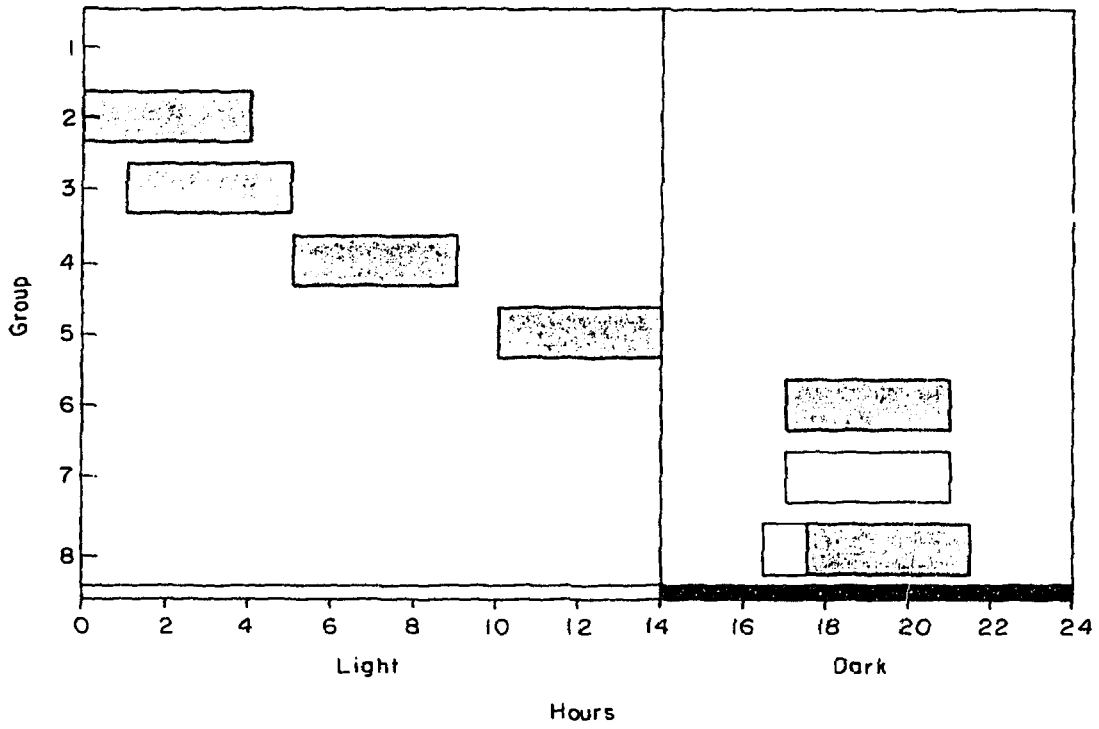

FIG. 1. Relationship of daily exposure periods to the 14:10; L:D cycle. Shaded bars represent the period when groups were exposed to 2260 lx light, open bars represent exposure to 65 lx of light. During non-exposure periods all groups remained in the animal room light cycle (65 lx) indicated by the open areas in the diagram. Note that animals in group 1 were not exposed in the exposure chamber.

TABLE II

Diurnal susceptibility of the rat retina to light-induced cell death, experiment 3

Group	*n*	ONL ± S.E.M. (μm)	TRT ± S.E.M.
1	5	35·5 ± 0·4*†‡	86·2 ± 1·6
2	4	21·9 ± 1·4†‡	78·8 ± 2·0
3	4	18·7 ± 1·3†	72·3 ± 3·3
4	5	27·3 ± 0·4*‡	85·8 ± 2·2
5	6	25·5 ± 0·7‡	78·6 ± 3·4
6	4	15·6 ± 2·3*†	58·1 ± 5·7
7	4	33·5 ± 1·6*†‡	82·4 ± 3·6
8	4	19·6 ± 1·9†‡	62·8 ± 2·7

See Materials and Methods for an explanation of groups and Fig. 1 for a diagram of the group exposure period relationships with the light cycle. Data analyzed by one-way *ANOVA with post-hoc Newman–Keuls* multiple range test. ONL = outer nuclear layer thickness; TRT = total retinal thickness. (*$P < 0.01$ vs. group 2; †$P < 0.01$ vs. group 4; ‡$P < 0.05$ vs. group 6.)

Experiment 1

Rats exposed to high intensity light beginning at light onset (group 2) had significantly reduced ONL thickness when compared to animals exposed during the middle of the light period (group 4, $P < 0.05$). Examination of the group mean ONL thickness at each of the twelve measurement sites (Fig. 2) revealed that the retinas of animals exposed at the beginning of the light period (group 2) had a thinner ONL

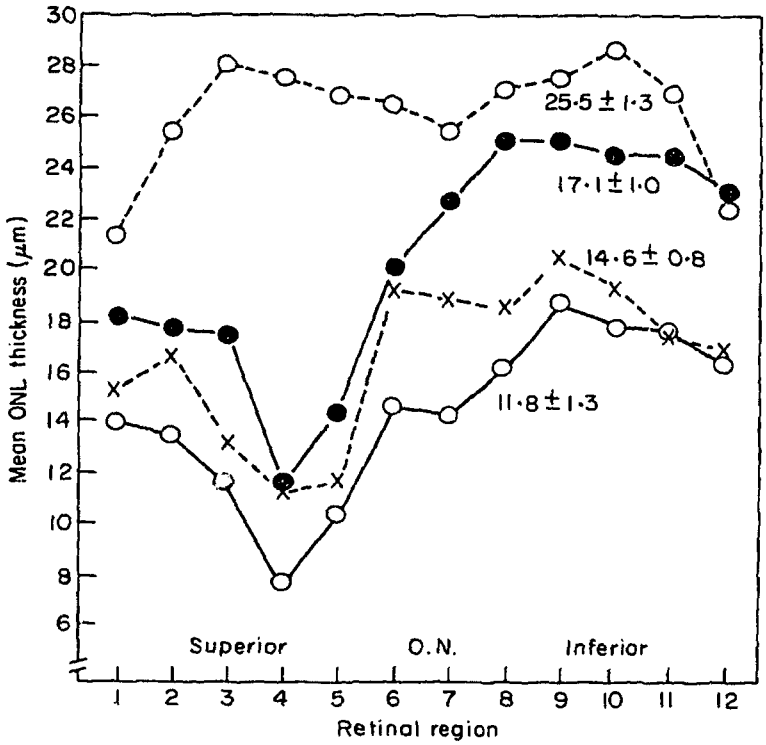

FIG. 2. Diurnal susceptibility: regional susceptibility to light damage (experiment 1). The pattern of ONL group mean thicknesses is shown for unexposed animals (O---O), and rats exposed to 4 hr day^{-1} for 8 days of 2260 lx light during the first 4 hr (O——O), middle 4 hrs (●——●), and last 4 hr (X---X) of the 14 hr light period. Twelve ONL thickness measurements separated by 450 μm were taken beginning at the ora serrata from superior peripheral retina (1) around to inferior peripheral retina (12). Adjacent values indicate overall group mean ONL thickness ±S.E.M. (μm). ($n = 4$ for all points.)

at every point peripherally and centrally in both superior and inferior hemispheres when compared to ONL thicknesses of rats exposed during the middle of the light period (group 4). The ONL thickness of rats exposed during the last 4 hr of the light period (group 5) was midway between values recorded for rats exposed during the middle of the light period and overlapped both groups in the regional pattern of retinal damage seen in Fig. 2. In all cases, the superior retina was more severely damaged than the inferior retina, as has been previously reported (Rapp and Williams, 1980).

Experiment 2

An additional group of rats was included in this experiment to control for the difference in the degree of dark adaptation between groups 2 and 4. Animals exposed at the beginning of the light period (group 2) were dark-adapted because they were removed from the animal room at light onset and immediately placed into 2260 lx illumination. The rats exposed during the middle (group 4) or end (group 5) of the light period were not dark-adapted because they were removed from the 65 lx illumination and then placed into high intensity light. Group 3 was included and exposed to 2260 lx light 4 hr day^{-1} beginning 1 hr after light onset to allow time for light-adaptation of the retina prior to high intensity light exposure. In this experiment, the retinas of rats exposed beginning at light onset (group 2), or 1 hr after light onset (group 3), were significantly more damaged than the retinas of rats exposed during the middle (group 4, $P < 0{\cdot}05$) or end (group 5, $P < 0{\cdot}05$) light period (see Fig. 3).

Retinas exposed beginning at light onset were more damaged than retinas that were exposed beginning 1 hr after light onset (group 2 vs. 3, $P < 0{\cdot}05$). In addition to groups of animals exposed during different phases of the light period, a group of animals was included in this and the subsequent experiment and was exposed to high intensity light during the middle of the dark period (group 6). To control for the lengthened daily total hours of light exposure (18 hr) received by these animals, another group of rats was exposed during the same period to 4 hr day^{-1} of 65 lx light (group 7). Therefore,

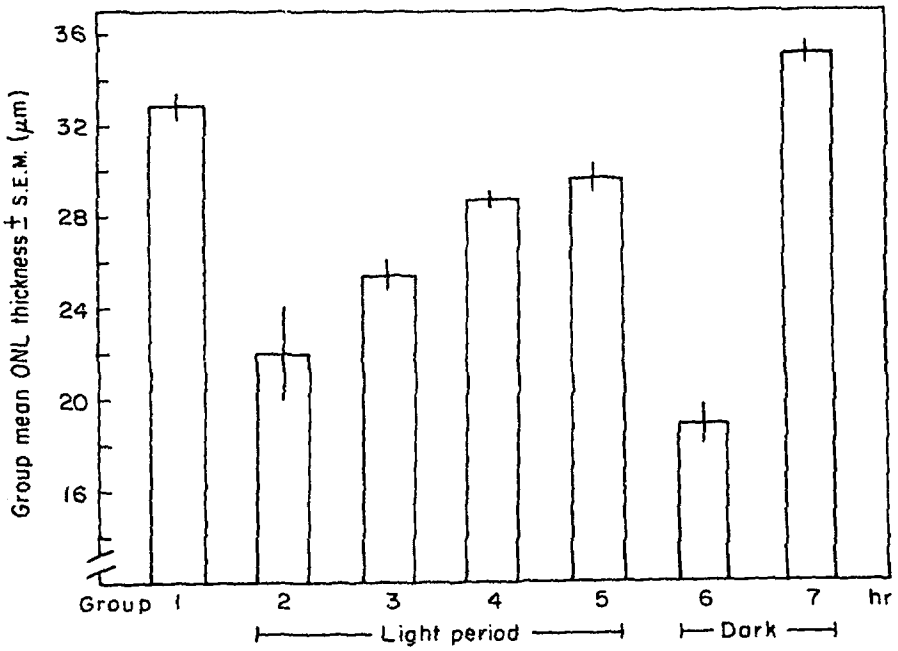

Fig. 3. Diurnal susceptibility to light-induced retinal damage (experiment 2) group mean ONL thickness ± S.E.M. for groups from experiment 2. Groups 1 and 7 were exposed to 65 lx of low intensity light. Groups 2–5 (see text) were exposed to high-intensity light (HLT) during the light period (see Fig. 1 for relationship of exposure periods to the light cycle). Group 6 was exposed to HLT during the middle of the dark period. Group 7 received 4 hr of exposure each day to low-intensity light during the middle of the dark period. Animals remained in 14:10 light cycle when not in the exposure chamber. (Group 1 vs. 2, 3 or 4, $P < 0{\cdot}01$; 1 vs. 5, $P < 0{\cdot}05$; 2 vs. 4, $P < 0{\cdot}01$; 3 vs. 5, $P < 0{\cdot}05$.) Data were analyzed by one way ANOVA with post-hoc Tukey's test. ($n = 3$, groups 2, 3, 4 and 6: $n = 4$, groups 1, 5 and 7.)

these animals received a 14:3:4:3; L:D:L:D light cycle for 8 consecutive days. At autopsy, rats exposed during the dark period were the most severely damaged of any exposed group (group 6 vs. 2, $P < 0{\cdot}05$), and had significantly thinner ONL thicknesses than did their controls kept in an extended light period (group 7, $P < 0{\cdot}001$). In fact, animals exposed to 4 hr day^{-1} of low intensity light during the middle of their dark period were not light damaged when compared to non-exposed 14:10, L:D controls (group 7 vs. 1, N.S. see Fig. 3).

Experiment 3 (Table II)

In agreement with the results obtained in experiments 1 and 2, the retinas of animals exposed during the first 5 hr of the light period (groups 2 and 3) were significantly more light-damaged than the retinas of animals exposed during the middle of the light period (group 4, $P < 0{\cdot}01$). Retinas of rats exposed beginning 1 hr after light onset

(group 3) appeared more light-damaged than rats exposed at the beginning of light onset; however, this difference was not statistically significant and was in contrast to the results of experiment 2. Also, in contrast to results obtained in experiment 2 but in agreement with results obtained in experiment 1, the retinas of rats exposed during the end of the light period (group 5) had ONL thicknesses that were midway between the results obtained for animals exposed at onset (group 2), and animals exposed during the middle of the light cycle (group 4). As in experiment 1, values obtained for group 5 were not statistically different from either group 2 or 4. As in experiment 2, the retinas of animals exposed to high intensity light during the middle of the dark period were the most significantly light-damaged (group 6 vs. 2, $P < 0{\cdot}01$). Again, a 65 lx intensity (14:3: 4:3; L:D:L:D) light regimen for 8 days did not result in a reduction in ONL thickness. Included in this experiment was a group of rats exposed to 4 hr of high intensity light during the middle 4 hr of the dark period which also received a 1 hr, 65 lx light exposure immediately preceding the onset of high intensity light. This group (8) was included for the same reasons as group 3, i.e. to control for the relative difference in dark-adaptation, but in this case between animals exposed during the light period (groups 2–5) and those exposed during the dark period (group 6). Animals light-adapted by the above procedure had a significantly thicker ONL at autopsy than did non-light-adapted, mid-dark exposed rates (group 6 vs. 8, $P < 0{\cdot}05$). Importantly, light-adapted, mid-dark exposed animals (group 8) were not significantly different in ONL thickness from animals which were exposed during the first 5 hr of the light period (group 8 vs. group 2 or 3, N.S.), but did have significantly thinner retinas than did animals exposed during the middle of the light cycle (group 8 vs. group 4, $P < 0{\cdot}01$).

4. Discussion

This series of experiments has demonstrated that the susceptibility of the rat retina to light-induced damage varies depending upon the period during the light cycle when animals are exposed to high intensity light. Rats exposed to high intensity illumination daily during the beginning of the light period either prior to or after light-adaptation, consistently had significantly thinner ONL thicknesses at autopsy than did animals exposed during the mid 4 hr of the photoperiod. The results obtained from rats exposed during the latter 4 hr of the light period varied, but suggested that animals may be less sensitive at the end of the light period than at the beginning. Rats exposed to high intensity illumination during the middle of the dark period were the most sensitive to light-induced photoreceptor cell death; however, the evidence above suggests that this sensitivity might have been related to the degree of dark-adaptation.

A number of functional processes related to the retina exhibit diurnal variation, and, therefore, may be involved in modulating the retinal sensitivity to light. During the light cycle there are known variations in retinal outer segment disc shedding (LaVail, 1976) and in the level of bleaching of the visual pigments or dark-adaptation. In addition, there are known circadian rhythms in circulating levels of hormones, including prolactin and adrenal–cortical hormones, both of which have been demonstrated to affect the degree of retinal susceptibility to photically induced damage.

Hormones and light damage

The level of circulating hormones may influence either the sensitivity of neuronal cells to the stimulus responsible for initiating cell death, or by some mechanism, may

affect the ability of the cell to endure the metabolic perturbation brought about by the primary stimulus. The stimulus which initiates cell death in the retina may be a direct effect of photic energy on retinal cells or some toxic by-product created as a result of the absorption of photic energy by the retina (see Noell, 1980). If the observed diurnal variation in retinal susceptibility is mediated by a circulating hormone, a minimum of two criteria must be met. First, the susceptibility of the retina to photically induced damage must be correlated with the levels of the hormone, and secondly, the hormone must be able to bind to retinal tissues.

Prepubertal hypophysectomy of rats protects the retina from the damaging effect of light exposure. Injection of exogenous prolactin (ovine) or crude pituitary gland homogenates or the transplant of a pituitary to the kidney capsule reverses the protection afforded by hypophysectomy (O'Steen and Kraeer, 1977). Therefore, prolactin is sufficient to modulate retinal susceptibility to photically induced damage. It has not been demonstrated whether prolactin exerts a direct effect on retinal photoreceptors or if prolactin has a specific function in the retina. O'Steen and Sundberg (1982) demonstrated autoradiographic patterns of isotope incorporation in retina, choroid and in the ciliary body after intracardial injection of iodinated ovine prolactin.

There is also evidence for a 24-hr variation in prolactin (Prl) levels in male rats (Dunn, Arimura and Scheving, 1972; Kizer, Ziven, Jacobowitz and Kopin, 1975). Other investigators have reported that the pattern of Prl secretion following ether stress does not vary during the day (Seggie and Brown, 1975, 1976; Taya and Igarashi, 1974). In summary, the investigations to date do not adequately support a circadian rhythm of resting Prl levels in the male rat. Recorded variations in Prl levels by some investigators may be related more to variations in the sensitivity of the Prl releasing mechanisms to stressful stimuli at different phases of the light–dark cycle. It follows that if variations in the levels of circulating Prl are related causally to the susceptibility of the retina to light-induced damage, the stimulus for the variations in Prl levels may be the differential response to stressors such as handling, novel environment or bright light at different times during the light cycle. It is plausible, therefore, that the pattern of retinal damage is related to the rhythm of the animals' susceptibility to stressful stimuli.

Well-documented adreno-cortical rhythms do exist in the male rat (Dunn et al., 1972; Guillemin et al., 1959; Krieger, 1979; Scheving and Pauly, 1966). Peak values of serum corticosterone occur late in the light period prior to the onset of the nocturnal activity period. The pattern of susceptibility to light damage, at least upon examination, correlates inversely with the adreno-cortical rhythm in that animals are least sensitive during the peak of the adrenal rhythm (groups 4 and 5) and more sensitive to damage when low levels of corticosterone are present (groups 2, 3 and 6). Recent evidence indicates that both stress and adrenalectomy influence retinal susceptibility to light-induced damage (O'Steen and Donnelly, 1982; Duncan et al., 1982). Therefore, ACTH and corticosterone may also play a role in modulating the susceptibility of retinal cells to photic damage.

Effect of dark-adaptation

Noell and Albrecht (1971) reported that dark-maintained rats were more sensitive to the effects of light exposure and demonstrated that when rats were dark-adapted for 24 hr prior to light exposure the protective influence of light rearing was maintained and dark-reared rats remained more sensitive to photic damage. Birch and

Jacobs (1980) have also reported that the retinas of rats raised in darkness are more sensitive to the damaging effects of light exposure than those of rats reared in a cyclic light environment. These studies indicate that long-term light history of an animal exerts a greater effect on retinal susceptibility than does short-term light history and provide evidence against a causal relationship between the pattern of retinal susceptibility and the degree of dark adaptation.

Animals exposed at the end of the light period (group 5) were not the least susceptible group, indicating the absence of a linear relationship between the time spent in the light period and susceptibility to light damage. Furthermore, light adaptation of animals at the beginning of the light period does not consistently reduce the susceptibility to light damage (group 3, experiments 2 and 3). Lastly, although the susceptibility of animals exposed during the middle of the dark period is reduced by a 1 hr light-adaptation (group 8), the animals remain significantly more susceptible than rats exposed during the middle or end of the light cycle (groups 4 and 5). Additionally, if the degree of short-term dark-adaptation does determine the susceptibility to light-induced damage, then rats should have been decreasingly susceptible as they spent more time in the light period. This evidence suggests that although dark-adaptation may play an important role in determining retinal susceptibility, some other influences must exert stronger and more consistent effects because the degree of dark-adaptation is not correlated directly with retinal sensitivity to light damage.

Retinal disc shedding

Whether the diurnal variation in retinal susceptibility is due to a mechanism involving the degree of dark adaptation, circulating hormone levels or retinal metabolic changes cannot be demonstrated conclusively by these experiments. If the variation in retinal susceptibility is due to some intrinsic rhythm, whether it be hormonal or retinal, the assumption is made that the controlling rhythm must remain intact and exert a constant influence throughout the 8-day exposure period. For this reason, animals were kept in the animal room for at least 8 days prior to the first day of light exposure to allow time for the light cycle to entrain hormonal and retinal rhythms. In addition, rats exposed to high intensity illuminance during the light period were arranged coincident with the normal light and dark onset which allowed no more than 14 hr total light daily. No attempt was made in this study to determine if normal hormonal cyclicity persisted during the exposure period.

It is important to note that the general pattern of retinal susceptibility was present despite differences in actual clock time of light onset between experiments (see Table I). This observation indicates that the mechanism which controls retinal sensitivity is linked tightly to the light–dark cycle and may suggest a light-entrained rhythm. These clock-time shifts in light onset required adjusted exposure schedules to maintain groups in the identical relationship to the L:D cycle.

In conclusion, these experiments have demonstrated a diurnal variation in the susceptibility of neurons to light-induced cell death. This variation in susceptibility is characterized by two periods: cells are more susceptible to damage during the dark period and in the early light period and less susceptible during the middle and at the end of the light period. This pattern of sensitivity to high intensity illumination is linked to the L:D cycle and not to clock-time suggesting an underlying circadian rhythm mechanism which at this time is unknown, but appears not to be related simply to the degree of dark-adaptation of an animal at the onset of exposure.

ACKNOWLEDGMENTS

This work was supported by Grant No. EY 02359 from NIH, National Eye Institute, and was submitted in partial fulfillment of the requirements for the Doctor of Philosophy Degree (T. E. D.).

REFERENCES

Ballowitz, L., and Dämmrich, K. (1972). Retinaschaden bei Ratten nach einer Fototherapie. *Z. Kinderheilk* **113**, 42–52.

Birch, D. G. and Jacobs, G. H. (1980). Light-induced damage to photopic and scotopic mechanisms in the rat depends on rearing conditions. *Exp. Neurology* **68**, 269–83.

Brawer, J. R., Schipper, H. and Naftolin, F. (1980). Ovary-dependent degeneration in the hypothalamic arcuate nucleus. *Endocrinology* **107**, 274–9.

Duncan, T. E. and O'Steen, W. K. (1982). The diurnal susceptibility of the rat retina to light-induced damage. *Anat. Rec.* **204**, 396–7.

Duncan, T. E. and O'Steen, W. K. (1983). The effects of acute stress on light induced retinal damage in the male rat. *Anat. Rec.* **209**, 504.

Duncan, T. E., O'Steen, W. K., Brodish, A. and Donnelly, J. E. (1982). Acute and chronic stress as modulators of light-induced retinal damage. *Anat. Rec.* **203**, 49–50.

Duncan, T. E., O'Steen, W. K. and Donnelly, J. E. (1982). Stress and light induced retinal degeneration. *Anat. Rec.* **202**, 143–4.

Dunn, J. D., Arimura, A. and Scheving, L. E. (1972). Effects of stress on circadian periodicity in serum LH and prolactin concentration. *Endocrinology* **90**, 29–33.

Friedman, E. and Kuwabara, T. (1968). The retinal pigment epithelium. IV. The damaging effects of radiant energy. *Arch. Ophthalmol* **80**, 265–80.

Gorski, R. A. (1971). Gonadal hormones and the perinatal development of neuroendocrine function. In *Frontiers in Neuroendocrinology* (Eds Martini, L. and Ganong, W. F.). Pp. 237–290. Oxford University Press, New York.

Guillemin, R., Dear, W. E. and Liebelt, R. A. (1959). Nycothemeral variations in plasma free corticosterone levels of the rat. *Proc. Soc. Exp. Biol. Med.* **101**, 394–5.

Kizer, J. S., Ziven, J. A., Jacobowitz, D. M. and Kopin, I. J. (1975). The nycothemeral rhythm of plasma prolactin: effects of ganglionectomy, pinealectomy, constant light, constant darkness, or 6-OH-dopamine administration. *Endocrinology* **96**, 1230–40.

Krieger, D. T. (1977). Regulation of circadian periodicity of plasma ACTH levels. *Ann. NY Acad. Sci.* **297**, 561–6.

Krieger, D. T. (1979). Rhythms in CRF, ACTH and corticosteroids. In *Endocrine Rhythms* (Ed. Krieger, D. T.). Pp. 123–42. Raven Press, New York.

Landfield, P. W., Baskin, R. K. and Pitler, T. A. (1981). Brain aging correlates: Retardation by hormonal-pharmacological treatments. *Science* **214**, 581–4.

LaVail, M. M. (1976). Rod outer segment disk shedding in rat retina: relationship to cyclic lighting. *Science* **194**, 1071–4.

LaVail, M. M. and Ward, P. A. (1978). Studies on the hormonal control of circadian outer segment disc shedding in the rat retina. *Invest. Ophthalmol. Vis. Sci.* **17**, 1189–93.

Lawwill, T. (1973). Effects of prolonged exposure of rabbit retina to low intensity light. *Invest. Ophthalmol.* **12**, 45–51.

Noell, W. K. (1980). Possible mechanisms of photoreceptor damage by light in mammalian eyes. *Vision Res.* **20**, 1163–71.

Noell, W. K. and Albrecht, R. (1971). Irreversible effects of visible light on the retina: role of vitamin A. *Science* **172**, 76–80.

Noell, W. K., Themann, H., Kang, B. S. and Walker, V. S. (1966). Functional and structural manifestations of a damaging effect of light upon the rat retina. *Fed. Proc.* **25**, 329.

Noell, W. K., Walker, V. S., Kang, B. W. and Berman, S. (1966). Retinal damage by light in rats. *Invest. Ophthalmol.* **5**, 450–72.

Olafson, R. P. and O'Steen, W. K. (1976). Hormonal influences on photoreceptor damage: the pituitary glands and ovaries. *Invest. Ophthalmol.* **15**, 869–72.

O'Steen, W. K. (1970). Retinal and optic nerve serotonin and retinal degeneration as influenced by photoperiod. *Exp. Neurol.* **27**, 194–205.

O'Steen, W. K. (1980). Hormonal influences in retinal photodamage. In *The Effects of Constant Light on Visual Processes* (Eds Williams, T. P. and Baker, B. N.). Pp. 29–49. Plenum, New York.

O'Steen, W. K., Anderson, K. V. and Shear, C. R. (1974). Photoreceptor degeneration in albino rats: dependency on age. *Invest. Ophthalmol. Vis Sci.* **16**, 940–6.

O'Steen, W. K. and Donnelly, J. E. (1982). Antagonistic effects of adrenalectomy and ether/surgical stress on light-induced photoreceptor damage. *Invest. Ophthalmol. Vis. Sci.* **22**, 1–7.

O'Steen, W. K. and Donnelly, J. E. (1982). Chronologic analysis of variations in two strains of rats after short term illumination. *Invest. Ophthalmol. Vis. Sci.* **22**, 252–5.

O'Steen, W. K. and Kraeer, S. L. (1977). Effects of hypophysectomy, pituitary gland homogenates and transplants, and prolactin on photoreceptor destruction. *Invest. Ophthalmol. Vis. Sci.* **16**, 940–6.

O'Steen, W. K. and Sundberg, D. K. (1982). Patterns of radioactivity in the eyes of rats after injection of iodinated prolactin. *Ophthalmic. Res.* **14**, 54–62.

Radnot, M., Jabbagy, P., Heszinger, I. and Lovas, B. (1969). Les données a l'ultrastructure de la rétine humaine sous l'effet de la lumière. *Opthalmologica* **159**, 460–71.

Rapp, L. M. and Williams, T. P. (1980). A parametric study of retinal light damage in albino and pigmented rats. In *The Effects of Constant Light on Visual Processes* (Eds Williams, Theodore P. and Baker, B. N.) Plenum, New York.

Rudeen, P. K. and O'Steen, W. K. (1979). The effects of the pineal gland on light-induced retinal photoreceptor damage. *Exp. Eye Res.* **28**, 37–44.

Scheving, L. E. and Pauly, J. E. (1966). Effect of light on corticosterone levels in plasma of rats. *Am. J. Physiol.* **210**, 1112–17.

Seggie, J. A. and Brown, G. M. (1975). Stress response patterns of plasma corticosterone, growth hormone and prolactin in the rat following handling or exposure to a novel environment. *Can. J. Physiol. Pharmacol.* **53**, 629–37.

Seggie, J. A., and Brown, G. M. (1976). Twenty-four hour resting prolactin levels in male rats: the effect of septal lesions and order of sacrifice. *Endocrinology* **98**, 1516–22.

Sisson, T. R. C., Glauser, S. C., Glauser, E. M., Tasman, W. and Kuwabara, T. (1970). Retinal changes produced by phototherapy. *J. Ped.* **77**, 221–7.

Taya, K. and Igarashi, M. (1974). Circadian rhythms in serum LH, FSH and prolactin levels in adult male rats. *Endocrinol. Japn.* **21**, 211–15.

T'so, M. O. M. (1973). Photic maculopathy in rhesus monkey. A light and electron microscopic study. *Invest. Ophthalmol.* **12**, 17–34.