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Trejo, LJ
Cicerone, CM

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RESEARCH NOTE

CHANGES IN VISUAL SENSITIVITY WITH AGE IN RATS WITH HEREDITY RETINAL DEGENERATION

LEONARD J. TREJO* and CAROL M. CICERONE†

Department of Psychology, University of California, San Diego, La Jolla, CA 92093, U.S.A.

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Abstract—Hereditary retinal degeneration in the Royal College of Surgeons (RCS) strain of rat has been shown to produce extensive loss of photoreceptors and a corresponding decline of the electroretinogram, ganglion cell sensitivity, and the sensitivity of the pupillary light reflex. The behaviorally measured thresholds of RCS rats, on the other hand, are reported to be comparable to those for age-matched controls. We report here, that our own behavioral measurements show a clear difference between RCS rats and age-matched controls between four to twelve months of age. The difference in thresholds between RCS and control rats is about three log units at four months of age, and this difference progressively increases until at twelve months, we measure threshold differences of over seven log units.

Retinal degeneration Visual sensitivity RCS rat

INTRODUCTION

Hereditary retinal degeneration in the RCS strain of rat produces extensive photoreceptor loss. Thinning of the outer nuclear layer and disappearance of photoreceptor outer segments begin in the first month of post-natal life and continue to the end of the third month (Bourne *et al.*, 1938; Lucas *et al.*, 1955; Dowling and Sidman, 1962; Noell, 1963). Histological assays estimate that more than 99% of the photoreceptors are lost and only a few photoreceptor somata, these lacking outer segments, remain in the retina beyond six months of age (LaVail *et al.*, 1974; Cicerone *et al.*, 1979).

It would be surprising if this pattern of degeneration at the photoreceptor layer did not produce large functional changes in the visual capacity of RCS rats. Indeed, the response of the retina as measured by the electroretinogram declines during the early postnatal months (Dowling and Sidman, 1962; Noell, 1963; Perlman, 1978; Kaitz and Auerbach, 1978).

Optic tract recordings also show progressive increases with age in the dark adapted thresholds of ganglion cells (Cicerone *et al.*, 1979). Single ganglion cells show an increase in threshold of over 3 log units during the first three to five months of life in the RCS rat. In addition, during this period an increasing number of ganglion cells appear to be driven by cones, not rods, when the eye is in a state of dark adaptation. This is likely to be related to the finding that a larger fraction of cones as compared to rods survive in the first few months of degeneration in the RCS eye (Cicerone *et al.*, 1979). Measurements of light reflex thresholds of the pupil in these animals agree closely with the electrophysiological results (Trejo and Cicerone, 1982).

In contrast, Kaitz (1976) found no change in the brightness detection thresholds of dark-reared RCS rats between 2.75 and 5.5 months of age. Additionally, for rats between 2.5 and 7 months of age her results suggest that there is no difference between light detection thresholds of dark-reared RCS and normal rats and a small (0.7 log unit) difference between RCS and normal rats raised in cyclic light. The only other behavioral study known to us measured light thresholds in older RCS rats, between 6 months and 2 years of age (LaVail *et al.*, 1974). This study was designed to demonstrate that RCS rats of advanced age could respond to light, and

*Present address: Human Factors and Organizational Systems Laboratory, Navy Personnel Research and Development Center, San Diego, CA 92152-6800, U.S.A.

†To whom correspondence should be sent at present address: Department of Psychology, Campus Box 345, University of Colorado, Boulder, CO 80309, U.S.A.

no direct comparisons to age-matched controls were made.

In view of the previously cited evidence which would appear to be consistent with much larger losses in visual sensitivity in RCS rats during the first six months than the values found by Kaitz (1976), we decided to obtain additional behavioral measurements of light detection thresholds in dark-reared RCS. We report here that our behavioral measurements show a large, progressive loss of visual sensitivity (over 3 log units) in RCS rats as compared to control animals during the first six postnatal months.

METHODS AND RESULTS

We used beige-hooded RCS rats descended by sibling-sibling mating from the original University College strain. We rejected one rat for bilateral microphthalmia, but saw no cataracts or other ocular anomalies in any of the rats we used. Unaffected albino (Sprague-Dawley) rats served as controls. All rats in this study were reared from birth in a dark room and were exposed to light only during cage cleaning (dim red overheads) and during training and testing (stimuli). Each rat fell into one of four age groups: 4 months, 6 months, 8-12 months, and 12+ months.

We trained and tested the rats in a light-tight Y-maze which was painted flat black inside. At the end of each of 3 arms of equal dimensions was a light source (Kodak Carousel projector), which uniformly illuminated a circular stimulus panel. The panel was made of translucent white plastic and was 4.0 cm in diameter. A micro-computer controlled the components of the maze, including shutters, shock scrambler circuit, infrared movement detectors, and a warning tone generator. Narrow band interference filters (Ditric Optics) and neutral density filters (Kodak) controlled the color and intensity of each stimulus and an electronic shutter (Uniblitz) controlled stimulus duration. The stimulus subtended 4.6 deg at the rat's eye and was of 500 msec duration. We connected the floor grids of the maze to the shock scrambler circuit which delivered 100-msec long pulses of 60-Hz alternating current. The current had a constant r.m.s. amplitude of 1 mA and the pulse repetition rate was 2 Hz. The infrared detectors in each arm detected the entry or exit of the animal.

Within each training or testing session the rats completed 6-12 blocks of 25 trials each.

Training and testing sessions both used the same schedule of reinforcement. During training every rat learned to complete a sequence of responses to escape shocks. Upon hearing the warning tone, the rat had 3 seconds to leave the starting arm, determine which of the other two arms contained a light stimulus, and enter the dark arm. If 3 sec elapsed before the rat left the starting arm, the computer began to deliver shocks at 2 Hz. The computer chose the arm that would contain the stimulus according to a pseudo-random sequence. If the rat entered the arm containing the light stimulus, the computer delivered six inescapable shocks in the presence of the tone and light during 3 sec then terminated the trial. A 2-sec time out was allowed before the next trial. If the rat entered the arm not containing the light stimulus, the computer turned the tone and light off. If shocks were occurring, the computer stopped them also. A 10-sec time out followed. The rat was free to enter any arm between trials. The arm the rat was in at the end of the timeout became the starting arm for the next trial. This schedule led to rapid learning and to errorless performance at suprathreshold levels within 3 training sessions.

Following initial training, each rat had at least three more training sessions using light intensities near threshold. Finally each rat had two or three testing sessions. In between the blocks of each session, the color filters were rotated from arm to arm, to avoid associations of color with position. The stimulus intensities were first lowered from above to below threshold and then presented again in reverse order. We computed the proportion of correct responses for a given stimulus intensity from the pooled performance of the rat over all of the testing sessions. We estimated thresholds from psychometric functions as the intensity at which 80% correct responses occurred.

Figure 1 shows mean thresholds for RCS rats and albino controls of different ages for light of wavelength 500 nm. By 4 months of age, RCS rat thresholds are elevated by 2.9 log units relative to controls (RCS: 5.85 ± 0.31 , Albino: 2.98 ± 0.22). By 6 months of age RCS thresholds are elevated by another 0.7 log units (6.56 ± 0.38) and by an additional 1.7 log units (8.21 ± 0.11) at 8 months. Although the rats in the 8 month age group were retested at 12 months of age, they could not detect the highest stimulus intensity produced by the apparatus (over 10.5 log quanta/sec/cm²) at the cornea.

Fig. 1. Mean detection thresholds for RCS (solid symbols) and albino control (open symbols) animals are shown. Light of 500 nm was used. Detection thresholds are indicated in terms of log quanta per second per cm^2 at the cornea. By 4 months of age, RCS rat thresholds are elevated by about 2.9 log units relative to controls (RCS: 5.85 ± 0.31 , Albino: 2.98 ± 0.22). By 6 months of age RCS thresholds are elevated by another 0.7 log units (6.56 ± 0.38) and by an additional 1.7 log units (8.21 ± 0.11) at 8 months. Although the rats in the 8 month age group were retested at 12 months of age, they could not detect the highest stimulus intensity produced by the apparatus (over 10.5 log quanta/sec/ cm^2 at the cornea). This was also found for a group of 15 month old RCS rats. In contrast, no significant increases in threshold were detected for controls at 10 months of age (3.02 ± 0.37) or at 19 months (3.00 ± 0.26).

This was also found for a group of 15-month-old RCS rats. In contrast, no significant increases in threshold were detected for controls at 10 months of age (3.02 ± 0.37) or at 19 months (3.00 ± 0.26).

In order to determine whether the behavioral thresholds we measured were based on rod or cone-mediated vision, we compared the thresholds measured with 500 nm light to those measured with 600 nm light. If thresholds are determined by a rhodopsin-based mechanism, then the predicted difference, based on a Dartnall nomogram curve (Ebrey and Honig, 1977) with a peak at 498 nm for rat rhodopsin (Bridges, 1959), is approximately 1.4 log units. The difference between thresholds for the 500 nm light as compared to the 600 nm light showed no significant change with age in our albino controls. The average difference for control animals was 1.27 ± 0.09 log units which is close to the value for rhodopsin. For RCS rats, the difference between thresholds for the 500 nm light as compared to the 600 nm light was 0.94 ± 0.08 log units at four months of age, 1.02 ± 0.08 log units at 6 months and 0.76 ± 0.03 log units at eight months. The difference at 8 months corresponds to a Dartnall nomogram curve with a peak at approximately

520 nm. This value is close to the spectral sensitivity for cones in the rat (Green, 1971; Birch and Jacobs, 1975; Cicerone, 1976). The values at 4 months and 6 months of age suggest that a combination of rod and cone mechanisms may set thresholds before 8 months of age in the RCS rat.

DISCUSSION

The results of this study agree with our earlier pupillometric data (Trejo and Cicerone, 1982) in showing a large progressive loss of visual sensitivity in dark-reared RCS rats with age. With the behavioral technique used here (shock avoidance), sensitivity declines linearly by about 0.5 log unit per month between 4 and 8 months. This rate is comparable to the rate observed using pupillometry over the same period (about 0.3 log unit per month). Electroretinograms and retinal ganglion cell recordings have also shown a large progressive sensitivity loss in dark-reared RCS rats. Dowling and Sidman (1962) found that visual thresholds as measured with the electroretinograms increased by 0.5 to 5 log unit between 30 and 60 days of age in the dark-reared RCS rat. Kaitz and Auerbach (1978) reported *b*-wave amplitude decreases in dark-reared RCS rats between 40 and 80 days of age at the rate of about 0.7 log unit per month. In dark-reared RCS rats Cicerone *et al.* (1979) found that over the first 5 months of age, sensitivity loss as measured by ganglion cell sensitivity progresses at the rate of about 1.0 log units per month. Densitometric measurements suggest an even higher rate of sensitivity loss. Perlman (1978) estimated the amount of regenerative rhodopsin as a function of age (20–90 days) in RCS rats. He found that the rhodopsin loss could be modeled as a linear process with a slope of about -1.4 log units per month.

We offer the following possible explanations for the higher rates of loss measured in single ganglion cells and by densitometry as compared to our pupillometric and behavioral methods. Some of the difference may be accounted for by adjustment for the period of measurement, since the rate of sensitivity loss progresses most rapidly in the first two to three postnatal months. Since behavioral, pupillometric, and electroretinographic thresholds presumably depend on an integrated response across large retinal areas, this may also account for part of these rate differences.

Although the rate of sensitivity loss in the

various studies cited are not exactly comparable, there is general agreement among the studies for a severe decline in visual sensitivity of RCS rats with age. This is in contrast to Kaitz's (1976) finding of no change in the behaviorally measured brightness detection thresholds of dark-reared RCS rats between 2.75 and 5.5 months of age. There are a number of procedural differences between our study and Kaitz's. First, we dark-adapted our animals for a minimum of 12 hr as compared to the 1 hr used by Kaitz. Dark adaptation proceeds very slowly in the rat and can require well over an hour even after partial bleaches (Cicerone, 1976; Perlman, 1978; Trejo and Cicerone, 1982). Second, Kaitz exposed her rats to a bright adapting stimulus before testing, and we did not. The combination of short dark adaptation and exposure to a bright adapting stimulus may have significantly light-adapted the rats in Kaitz's study. Indeed, Kaitz's reported thresholds for albino controls are approximately 1.6 log units higher than what we obtain, and this difference is consistent with photopic determination of thresholds in Kaitz's study. It seems possible that photopically mediated sensitivity may show less change, since in RCS rats retinal degeneration has been shown to produce more rapid rod loss than cone loss in the first six postnatal months (Cicerone *et al.*, 1979).

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