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Compensatory synaptic growth in the rod terminals as a sequel to partial photoreceptor cell loss in the retina of chimaeric mice

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Summary

In the retina of chimaeric mice of *rd* and wild-type genotypic combination, selective loss of *rd/rd* photoreceptor cells, after initial development, leads to a mosaic retina with variable amounts of normal photoreceptor cells present over the retinal surface. In some of the rod terminals of these retinas the synaptic complexes with the second order retinal neurons are seen to contain multiple synaptic ribbons and an increased number of profiles of the postsynaptic elements. These changes are observed only in the rod terminals and not in the cone pedicles. Computer aided three-dimensional reconstruction of the altered synapses shows that these changes result from an increase in the number of synaptic sites, characterized by multiplication of the synaptic ribbons and enlargement of the second order neuronal processes. A quantitative analysis of such synapses, based on serial electron micrographs, shows that these are most frequently located in the retinal regions of the chimaeric individuals that have suffered maximum photoreceptor cell loss. Thus synaptic growth appears to take place as a reaction to the reduction of afferent input to the postsynaptic components. These findings demonstrate persistent synaptic plasticity in the rod terminals of mammalian retina during the maturational phase of late postnatal development. Compensatory synaptic growth in the rod terminals, as recorded here, can have important implications for the maintenance of visual sensitivity in the diseased or ageing retina.

Key words: photoreceptors, rod synapses, synaptic plasticity.

Introduction

An impulse generated by light in the rods and cones is transmitted to the second order retinal neurons across the synaptic junctions. Nerve cells in relay carry the impulse through the optic nerve to the various brain centres. Experimental ablation at specific sites has been used to demonstrate synaptic plasticity and regenerative ability at the level of the cortex (Kaas et al., 1990), optic tectum (Lund and Harvey, 1981), and ganglion cells (Perry and Linden, 1982). It remains to be seen if any reactive compensatory mechanism can operate in the photoreceptor terminals. In this study we examine whether the synapses in the normal rod terminals show a comparable plasticity after partial photoreceptor cell loss.

Slow and progressive retinal degeneration is known to occur in mice afflicted by the *rds* gene (Van Nie et al., 1978) so that a part of the depleting population of photoreceptor cells survive in the retina of relatively older mice before their complete elimination. Photoreceptor cells are also known to be selectively damaged by constant exposure to light (Noell et al., 1966) and a partial loss of photoreceptor cells can be achieved by a relatively brief exposure. In both of these instances a proportion of the surviving rod cells, but not the cones, have been observed to enlarge the area of their synaptic contacts after these insults (Jansen and Sanyal, 1984, 1987). In mice homozygous for the *rd* gene rapid loss of photoreceptor cells occurs during the early postnatal period (Tansley, 1951; Sidman and Green, 1965). In the retina of chimaeric mice of *rd/rd* and wild-type genotypic combination, selective loss of *rd/rd* photoreceptor cells leads to a variable mosaic distribution in the numbers of normal photoreceptor cells in different regions of the retina. In the present study the outer plexiform layer located under these regions was examined with the electron microscope for synaptic changes and their relation to photoreceptor cell loss. In this layer the photoreceptor terminals make synapses with the second order retinal neurons, i.e., the bipolar cell dendrites and the horizontal cell processes. Using computer aided reconstruction and morphometry we show here that a proportion of the remaining rod cells

multiply their synaptic sites and that the frequency of such terminals is related to the degree of photoreceptor cell loss.

Materials and methods

Chimaeric mice

Pigmented C3H mice that are homozygous for the *rd* gene and albino BALB/cHeA mice that carry the normal allele, provided the materials of *rd/rd* and +/+ genotypes respectively. Chimaeric mice were produced by aggregation of morulae. Spontaneously ovulating females were allowed to mate and were then killed after 48 hours. A combination of procedures described by Mintz (1971a) and Tarkowski (1964) was used to produce aggregated morulae as described earlier (Sanyal and Zeilmaker, 1976). Briefly, two 8-cell embryos of two different genotypes were aggregated in a drop of culture medium in oil with the aid of a micro-manipulator. Single blastocysts, resulting from the composite morulae, were transferred to the uterine horns of recipient females on day 2 of pseudopregnancy, the day of sterile mating plug being counted as day 0. Pregnant recipients were allowed to come to term, chimaeric individuals were identified by the presence of mixed coat colour and used after a survival period of 2 months.

Animals were maintained in 12-hourly cyclic light and dark periods with unlimited access to food and water under standard housing conditions. Animals were used in compliance with the Experiments on Animals Act of the Netherlands, in agreement with the ethical consideration included in the European Convention for the Protection of Vertebrate Animals.

Histology, light microscopy

The eyes were fixed in an aldehyde mixture and postfixed in osmium tetroxide as described earlier (Jansen and Sanyal, 1984). During dehydration small pieces of the central retinal regions in the posterior pole were taken out and embedded in low viscosity epoxy resin (Spurr, 1969). Semithin sections were stained in toluidine blue and examined by light microscopy. Estimates of the loss of photoreceptor cells were made by counting the rows of nuclei present in the outer nuclear layer.

Electron microscopy, three-dimensional reconstruction

Retinal regions within the block face showing a definite proportion of the outer nuclear layer were used for electron microscopy. Serial ultrathin sections, numbering 30 to 40 in a row, were attached to formvar coated slot grids and stained in uranyl acetate and lead citrate (Reynolds, 1963). Serial electron micrographs of the outer plexiform layer region were made from all the sections in a series.

The three-dimensional reconstruction of the synaptic complex with multiple ribbon was undertaken with the help of a computer programme (MacReco 3.2, originally devised by E. Otten, State University of Groningen, the Netherlands). The contours of the various components of a synaptic profile, encompassed in successive sections were fed into a computer and a three-dimensional image was produced. The programme further allowed viewing of the entire complex from different angles as well as viewing in sectional and partial representations.

Electron microscopy, quantification

Profiles of each of the rod terminals present in the series were followed through the successive electron micrographs and the number of discrete synaptic ribbons present within the synaptic complex was recorded. The frequency of rod terminals with multiple ribbons in each chimaeric individual was calculated as a percentage of the total and used for comparison between the experimental groups. Information about the total number of chimaeric mice and lengths of retinal tissue examined are given in Table 1. Student's *t*-test was used for the evaluation of the statistical significance of the data.

Table 1. *The relative frequency of rod terminals containing multiple synaptic ribbons (SR) in the retina of 15 chimaeric mice with variable number of rows of photoreceptor cells in the outer nuclear layer (ONL)*

Animal no.	Rows ONL	Number of terminals with one SR	Number of terminals with multiple SR	% terminals with multiple SR	Mean± s.e.m.
299	8-10	19	0	0.0	
302		16	4	20.0	
233		20	6	23.1	
277		17	0	0.0	
273		15	1	6.3	9.9±4.9
271	5-7	14	1	6.6	
306		17	10	37.0	
269		16	2	11.1	
270		19	4	17.4	
276		25	0	0.0	14.4±6.3
272	2-4	6	13	68.4	
300		5	13	72.2	
301		4	10	71.4	
291		6	9	60.0	
303		1	15	93.7	73.1±5.6

A constant frame of 25 μm long linear stretch of OPL located in 30-40 serial sections was used as sample. All rod terminals encompassed within these samples were included in the counts. For regions with 8-10 rows of outer nuclei 2 such series were used and for regions with lesser rows of outer nuclei 3 series were used.

Results

Light microscopy

The retinas in the two genotypes appear indistinguishable until 10 or 11 days after birth (Fig. 1A,B), although death of photoreceptor cells has already started by then in the retina of *rd/rd* mice (Sanyal and Bal, 1973). From this stage on, a very rapid loss of photoreceptor cells in the *rd/rd* retina results in an extreme reduction at 3 weeks, and eventually in almost complete elimination of the Outer Nuclear Layer (ONL) at 2 months (Fig. 1C). In the normal retina a fully differentiated layer of the photoreceptor cells with about 10 rows of perikarya in the ONL is clearly present (Fig. 1D).

In the eyes of 2-months-old chimaeric individuals the photoreceptor cell population, marked by the thickness of the ONL, was variably reduced, as shown in previous studies (Mintz and Sanyal, 1970; LaVail and Mullen, 1976; Sanyal and Zeilmaker, 1976). The surviving photoreceptor cells of normal genotype were present in

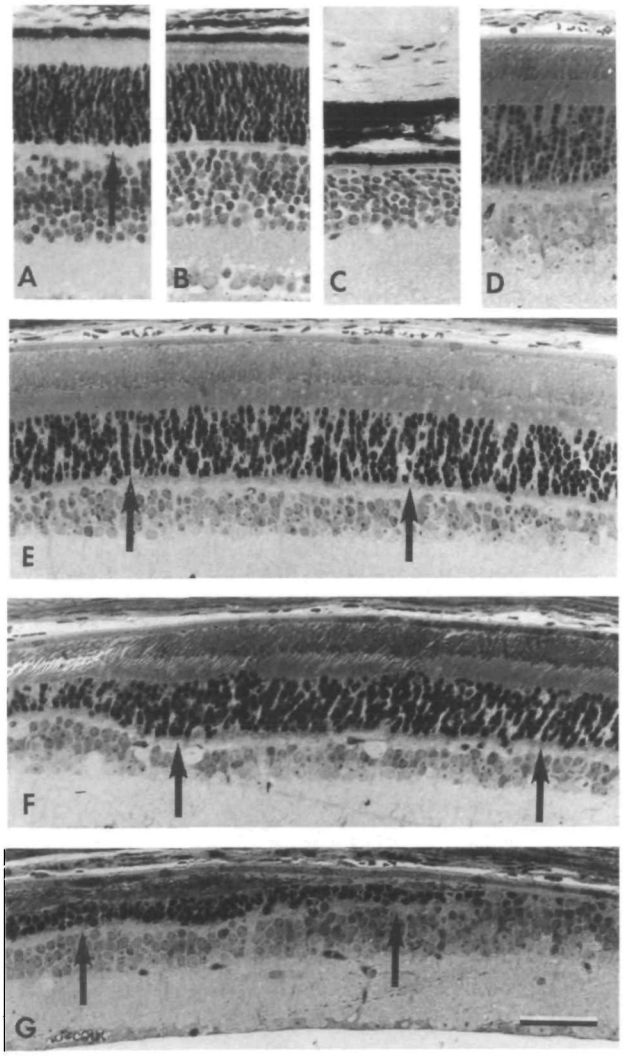

Fig. 1. (A) Retina from a 10-day-old mouse that is homozygous for the *rd* (retinal degeneration) gene; at this stage of retinal development the photoreceptor cells have started differentiating their receptor and synaptic elements and their perikarya are completely separated in the outer nuclear layer (arrow); the retina is similar to the retina of a normal (+/+) mouse of the same age (B). (C) Retina from a *rd/rd* mouse at 2-months-old; rapid degeneration of photoreceptor cells has almost completely eliminated the outer nuclear layer, the inner retinal layers remaining intact. (D) Retina from +/+ mouse at 2-months-old. Retinal sections from 2-month-old chimaeric mice show regions (arrows) with 8-10 rows of photoreceptor cell nuclei (E) as in the retina of normal mice and also regions with 5-7 (F) or 2-4 (G) rows of photoreceptor-cell nuclei due to the selective degeneration of *rd/rd* cells. Bar=25 μm.

variable numbers of rows in the ONL of the retinas of such chimaeric mice depending on the proportion of the *rd/rd* photoreceptor cells that were initially present in the developing retina and were eventually lost from the adult retina. For the purpose of this study three types of retinal regions were distinguished: (1) regions with 8-10 rows of outer nuclei (Fig. 1E), similar to normal retina and having suffered minimal photoreceptor cell loss, serving as a reference for comparison, (2) regions with 5-7 rows of outer nuclei (Fig. 1F) having suffered moderate loss, and (3) regions with 2-4 rows of outer nuclei having suffered severe photoreceptor cell loss (Fig. 1G). Although retinal regions with variable proportion of ONL were present in the same eye or even in the same section, such regions were often located in small patches and were very much intermingled. However, in chimaeras with relatively more normal photoreceptor cells, retinal regions with 8-10 rows of outer nuclei were more extensive. Similarly, in chimaeras with relatively less normal photoreceptor cells regions with 5-7 or 2-4 rows of outer nuclei were more extensive. Therefore, retinal samples from the chimaeras were first examined by light microscopy and extensive areas of retina with requisite numbers of rows in the ONL were identified. The Outer Plexiform Layer (OPL) located in the centre of such retinal regions was studied by electron microscopy.

Electron microscopy

Since rods constitute 97% of the retinal photoreceptors in mice (Carter-Dawson et al., 1978), the receptor terminals entering the OPL originate largely from the rods. Each rod terminal, called a spherule, typically contains a single synaptic complex, marked by one centrally located Synaptic Ribbon (SR). Pedicles or cone terminals are only infrequently encountered, and have a disc shaped form and contain many separate synaptic complexes (Dowling, 1987). A part of the OPL from a chimaeric retina is shown in Fig. 2. Of the several rod terminals present in this frame, a few have a synaptic profile with one SR and a few others appear to have no SR, as would be expected from chance variation in the plane of section. In addition, rod terminals are present in which the synaptic complex appears larger in size and contain more than one SR. In a typical rod terminal a single SR is in the centre of a single synaptic complex (Fig. 2B). In a terminal with additional (multiple) SR (Fig. 2C) each SR is seen as a centre of a distinct synaptic site.

The exact microanatomical relationship of the various structures in such synaptic complexes were further analyzed in reconstructions from electron micrographs of serial sections. In the computer generated three-dimensional image of a normal synapse, the single SR is seen as one elongated plate marking the median plane of the synapse (Fig. 3A). One process of the horizontal cell is located on each side of the SR (Fig. 3B), and the bipolar cell dendrite is aligned along the inner edge of the SR; a second bipolar cell dendrite is also present (Fig. 3C). All four elements from the second order neurons can be seen to leave the rod terminal. This reconstucted image of a normal appearing rod synapse from a chimaeric retina is in all respects comparable to a similar image of the normal synapse from a wild-type mouse.

In the three-dimensional view of a synaptic complex containing multiple SR, each SR is seen as a separate element, marking the centre of separate synaptic sites (Fig. 3D-F). However, four processes originating from

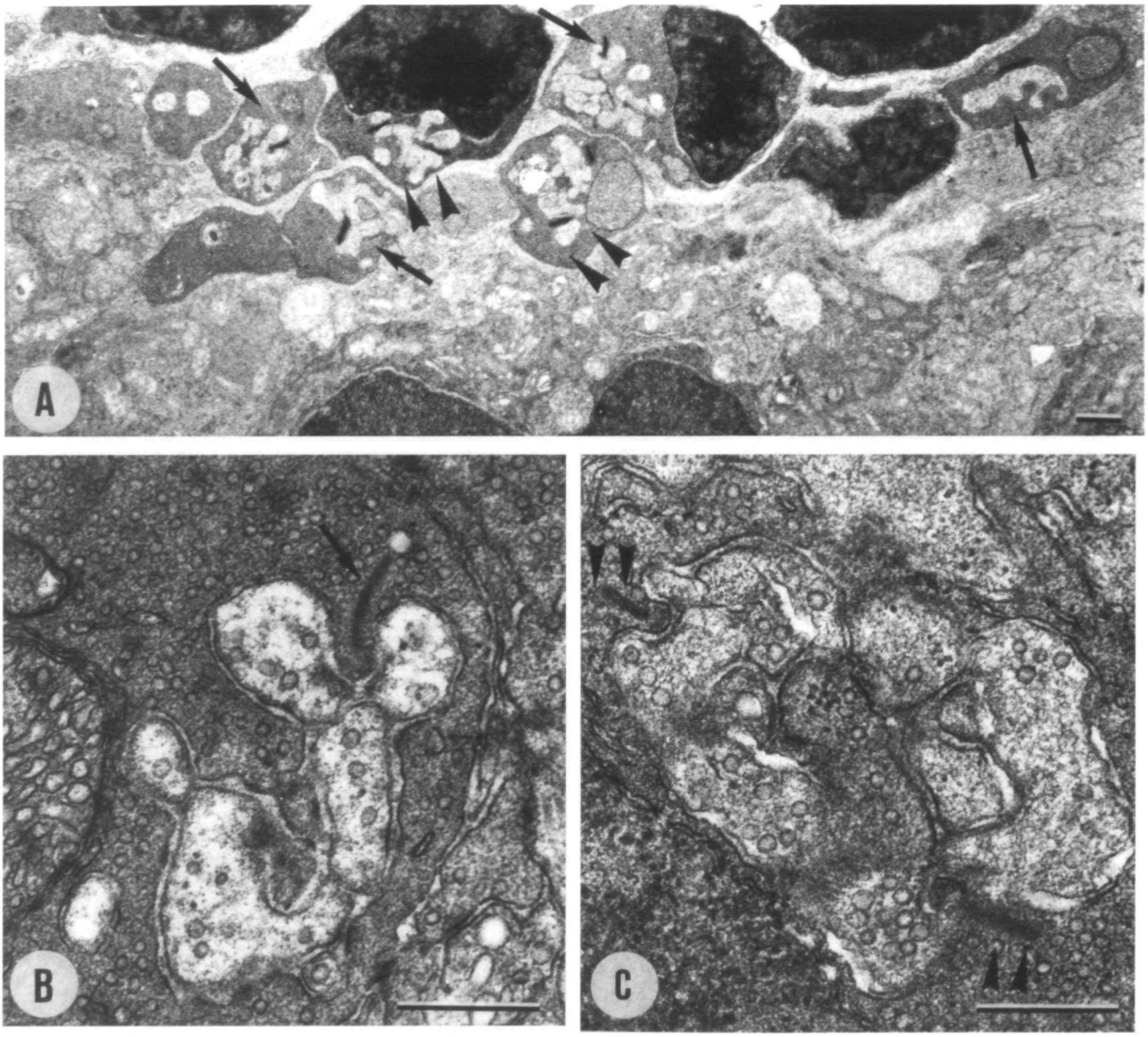

Fig. 2. (A) Electron micrograph of the outer plexiform layer of the retina from a chimaeric mouse showing rod terminals with synaptic profiles containing one (arrow) or more than one (arrowheads) synaptic ribbons. (B) Enlarged view of a typical rod synapse with a single synaptic ribbon (arrow) flanked laterally by horizontal cell processes and facing a bipolar cell dendrite. (C) Enlarged view of a rod synaptic complex with multiple synaptic ribbons (double arrowheads); each of these appears as centres of separate synaptic sites. Bar=0.5 μm.

the second order neurons enter the terminal, as in a normal spherule. These processes branch to, or participate in the different synaptic sites, so that each site has the same structural components as a normal synapse. Thus, multiplication of the synaptic sites has taken place in some of the rod terminals through a process of growth and proliferation of the existing components, and the increase in the number of rod terminals with multiple SR is a measure of this process.

Quantitative data

The exact number of SR in each rod terminal in a sample of the OPL was determined using serial electron micrographs. The relative frequency of rod terminals with multiple SR (Table 1) was lowest in samples of the OPL, located under ONL region (1) containing 8-10 rows of photoreceptor nuclei. In the five chimaeric individuals included in this group, the frequency varied between 0 and 23.1% with a mean of 9.9%. In samples of OPL, located under ONL region (2) containing 5-7 rows of photoreceptor nuclei, taken from five other chimaeric individuals, the frequency of terminals with multiple SR was only slightly higher and the difference was not significant. However, a six- to seven-fold increase in the frequency of rod terminals with multiple SR was recorded in the samples of OPL located under ONL region (3) containing 2-4 rows of nuclei. Some differences were found between the five chimaeric individuals belonging to this group; the mean frequency

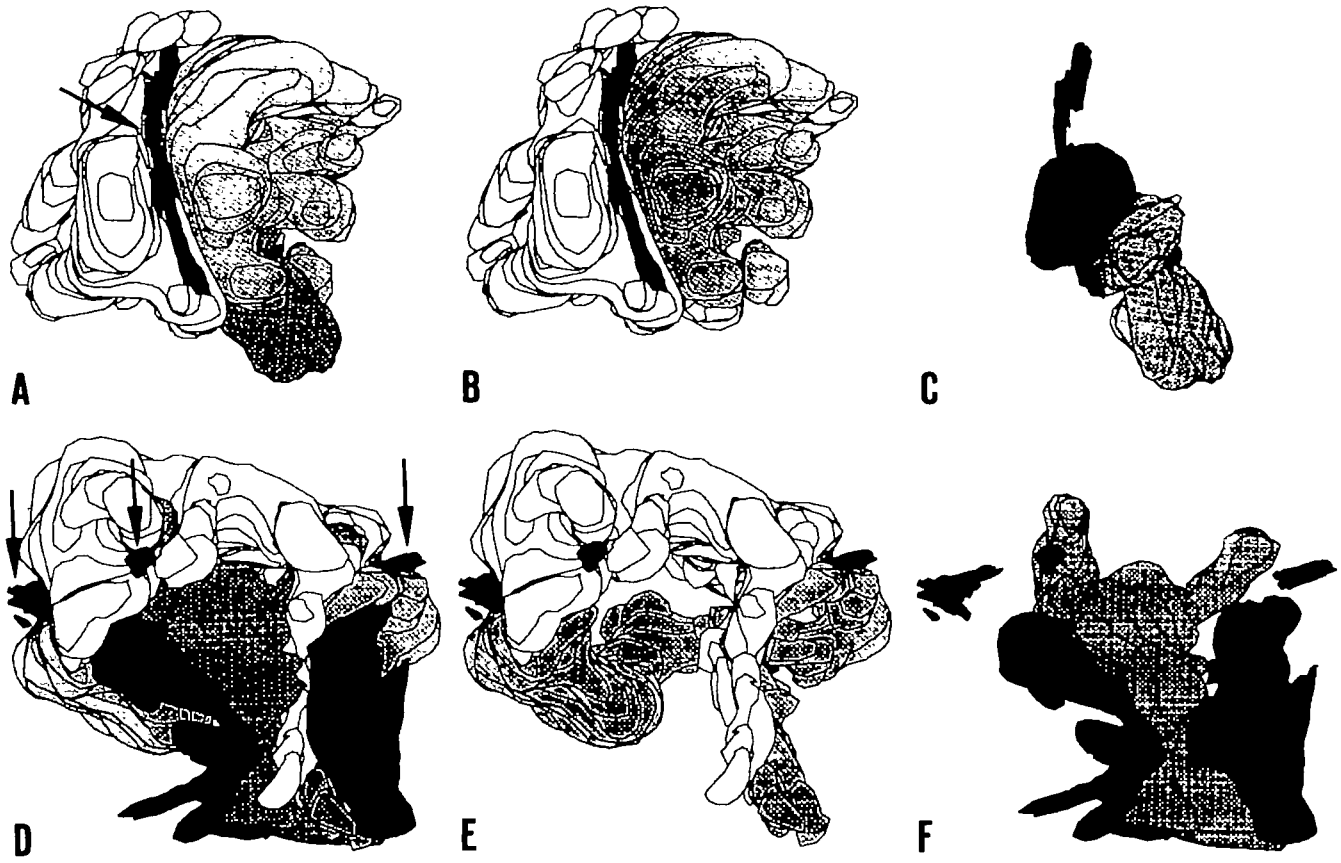

Fig. 3. Printouts from a computer-generated three-dimensional view, reconstructed from serial electron micrographs, showing the synaptic ribbon (arrow) and the second order neuronal components participating in the rod synapse of chimaeric mice. (A) Total view of the components in a typical normal synapse (B), the two horizontal cell processes and (C), the two bipolar cell dendrites in relation to the alignment of the synaptic ribbon. (D) Total view of the components of an altered synapse with multiple synaptic ribbons (arrows) as centres of multiple synaptic sites; (E), separate view of the two horizontal cell processes and (F), the two bipolar cell dendrites in relation to the multiple synaptic ribbons.

of rod terminals with multiple SR was 73.1%. The difference with group 1 and group 2 was highly significant (Student's *t*-test, $P \leq 0.001$). Thus an increase in the number of synaptic sites within the terminals of the surviving population of rod photoreceptors is most frequently observed in the retinal regions that have suffered maximal photoreceptor cell loss.

Discussion

The cellular phenotype in a genetically mosaic tissue, such as appears in a chimaeric mouse, can be variously affected, depending upon the specific developmental effect of the gene (see Mintz, 1971b; McLaren, 1976 for general review). Recent studies have established that the *rd* gene in mice codes for the β-subunit of the photoreceptor cell specific phosphodiesterase (Bowes et al., 1989, 1990). In the homozygous mutants, malfunction of this enzyme leads to a high concentration of cyclic GMP that cause selective degeneration of the photoreceptor cells (Farber and Lolley, 1974). Rods are affected earlier and degenerate faster than the cones (Carter-Dawson et al., 1978), and all photoreceptor cells, as well as any indication of visually evoked cortical function, disappear before the age of two months (Dräger and Hubel, 1978). The inner retinal layers, particularly the bipolar cell population (Blanks and Bok, 1977), remain apparently unaffected. Previous findings in the retina of chimaeric mice have shown that the expression of the *rd* gene is autonomous, i.e., independent of the genotype of the neighbouring cells (Sanyal and Zeilmaker, 1984; Sanyal, 1987). Therefore, it can be inferred that the retina of *rd/rd* ↔ +/+ mice at the age of two months, when all *rd/rd* photoreceptor cells have disappeared, is an otherwise normal retina in which the photoreceptor cell population is variably reduced over the retinal surface.

The synaptic changes in the chimaeric retina are similar to those previously observed in the *rds* mutant (Jansen and Sanyal, 1984) and light damaged retina (Jansen and Sanyal, 1987) and consist mainly of the occurrence of rod terminals with multiple SR and increased number of profiles of the second order neurons. Electron microscopy on serial sections has

further shown that each of these multiple SR in the rod terminals of chimaeric retina is the centre of a separate synaptic site. In the rod terminals of the mammalian retina a single SR marks the centre of a single synaptic site. Although some difference in the length or form of the SR may be observed, occurrence of any diurnal variation of physiological significance appears to be uncertain (McCartney and Dickson, 1985). However, the prevailing view of the function of SR, speculated earlier (Bunt, 1971), that these organelles may facilitate transport of synaptic vesicles to the specific site of the presynaptic membrane is in keeping with the correlation in the emergence of multiple SR and multiple synaptic sites recorded in the present study.

The second order neuronal processes participating at these multiple sites have grown out of the normally present components in the original single synaptic unit. Thus it can be concluded that normal rod terminals in mice possess synaptic plasticity that results in growth in response to partial photoreceptor cell loss. It is noteworthy that the highest frequency of rod terminals showing such synaptic growth is encountered in the retinal regions that have suffered maximal photoreceptor cell loss and that in these regions the majority of the rod terminals have multiple synaptic sites.

In the retina of *rd/rd* mice degeneration is most rapid during postnatal days 12 and 14 when the photoreceptor cell population is reduced to less than half (Tansley, 1951); thereafter degeneration continues slowly so that around day 21 a single row of cone perikarya is still present (Carter-Dawson et al., 1978). In the retina of normal mice synaptic contacts between the photoreceptor cells and the second order retinal neurons are established largely during the second and third weeks of postnatal life (Blanks et al., 1974a; Sanyal and Jansen, 1989). In the retina of *rd/rd* mice, photoreceptor synapses are developed during the same period, although these are less frequently encountered in the mutant retina than in the normal retina (Blanks et al., 1974b), presumably as a result of reduction in the photoreceptor cell population due to degeneration. Thus the period of rapid photoreceptor cell loss coincides with the period of postnatal development when synaptogenesis between the photoreceptor cells and the second order retinal neurons is nearing completion. In the retina of chimaeric mice selective loss of *rd/rd* cells will thus produce a variable degree of reduction in the presynaptic components and partial functional deprivation of the proximal parts of the visual system.

In the mammalian retina many rods are presynaptic to multiple dendritic ends of a few bipolar and horizontal cells, while a single cone pedicle is presynaptic to a number of such cells (Boycott and Kolb, 1973; Kolb, 1977; Kolb and Nelson, 1983). Partial loss of rods will lead to reduced signal input. An increase in the number of synaptic sites in the remaining rod terminals can be expected to compensate for this loss. In this respect the process of synaptic growth in the rod terminals is comparable to the process of reactive synaptic growth and regeneration following partial deafferentation as previously described in other parts of the central nervous system (Cotman and Lynch, 1976). In a number of studies morphological growth of synapses has indeed been shown to result in increased sensitivity (Fields and Ellisman, 1985) or sensory restitution (Hoy et al., 1985).

Rods are responsible for scotopic vision. An optimal level of impulse, transmitted to the second order neurons, is essential for the maintenance of visual sensitivity. Drastic or chronic photoreceptor cell loss is known to occur in patients suffering from retinitis pigmentosa (Voaden, 1991), senile macular degeneration (Sarks, 1976) or in ageing individuals (Gartner and Henkind, 1981). Compensatory synaptic growth in the rod terminals can conceivably help to maintain a functional degree of visual sensitivity over a longer period of life of the afflicted individuals. An experimental approach to further elucidation of this phenomenon should be rewarding.

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