Photoreceptor Death, Trophic Factor Expression, Retinal Oxygen Status, and Photoreceptor Function in the P23H Rat

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Purpose. To relate the oxygen environment of the retina to photoreceptor stability, protection, and function in the P23H rat.

Methods. Heterozygote P23H-3 (Line 3) rats were studied. Photoreceptor death rates were assessed with the TUNEL technique for detection of fragmenting DNA, in a developmental series from postnatal day (P)16 to P105 (adult). In adult retinas, trophic factor status was assessed with immunohistochemistry, intraretinal oxygen environment with O2-sensing electrodes, and photoreceptor function by the flash-evoked, dark-adapted electroretinogram (ERG), recorded in anesthetized animals.

Results. Photoreceptor death begins by P16; peaks at P25, when the frequency of TUNEL profiles exceeds 70/mm of retina; and then declines to low (<5/mm) adult rates. Compared with that in nondegenerative Sprague-Dawley (SD) rats, the rate of photoreceptor death is abnormally high from P16 and remains several-fold higher than normal into young adulthood. In addition, the outer nuclear layer is reduced to approximately half of control thickness, and the levels of ciliary neurotrophic factor (CNTF), glial fibrillary acidic protein (GFAP), fibroblast growth factor (FGF)-2, and FGF-2/FGFR1 colocalization are markedly upregulated. O2 tension and uptake are relatively normal in the inner retina, but uptake is considerably reduced, and O2 tension is significantly raised in the outer retina. Surviving photoreceptors generate an a-wave with normal peak latency but sharply reduced amplitude.

Conclusions. Excess photoreceptor degeneration in the P23H-3 retina begins just after eye opening, peaks in early postnatal life, and then slows, but persists into adulthood. In the adult retina, surviving photoreceptors operate in an environment that is chronically hypoxic (and therefore toxic) and in which protective factors (CNTF, FGF-2) are chronically upregulated. The net result, slow degeneration and degraded function in an environment that is both toxic and protective, may be representative of adult photoreceptor status in a number of human retinal degenerations. Hyperoxia-induced photoreceptor death may be a self-reinforcing factor that increases oxidative stress in surviving photoreceptors. (Invest Ophtalmol Vis Sci. 2004;45:2013–2019) DOI:10.1167/iovs.03-0845

In previous studies, we have explored the effects of photoreceptor depletion on environmental aspects of the surviving photoreceptors, including the expression of trophic factors, the rate of on-going photoreceptor death, the expression of functional molecules, the electroretinogram, and the oxygen status of the retina (its rate of oxygen consumption, and tissue oxygen levels).1-5 In the current study, we explored photoreceptor death, trophic factor (CNTF, FGF-2) expression, oxygen status, and photoreceptor function in the P23H-3 rat, a model of an autosomal dominant rhodopsin-mutant form of human retinitis pigmentosa (Steinberg RH, et al. J OVS 1996;37:ARVO Abstract 3190).6,7 The results show early onset of the degeneration, soon after eye opening. By young adulthood, the degeneration of photoreceptors has slowed but is continuing, the outer retina is chronically hypoxic and rich in stress-inducible, protective proteins, and the ERG is sharply reduced.

Methods

All procedures were in accord with the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research.

Strains and Rearing Conditions

P23H-3 homozygous animals were obtained from the UCSF School of Medicine, Beckman Vision Centre. Those used in the present experiments were heterozygotes, the offspring of mating P23H-3 homozygotes with SD control animals. All rats were born and bred in the University of Sydney animal facility under dim cyclic light (12 hours at <5 lux, 12 hours in the dark). Rats used for intraretinal oxygen measurements were reared until P60 to P80 as above, when they were transferred to the Lions Eye Institute in Perth, where they were kept in brighter conditions (12 hours at ~50 lux, 12 hours in the dark) until they were used for studies of intraretinal oxygen levels. The animals were fed standard laboratory rat chow with water provided ad libitum.

TUNEL Labeling Immunohistochemistry

Eyes were immersion fixed in 4% paraformaldehyde in PBS buffer at pH 7.4 and 4°C for 1 to 3 hours. After three rinses in 0.1 M PBS the eyes were left overnight in a 15% sucrose solution to provide cryoprotection. Eyes were embedded in mounting medium by snap freezing in liquid nitrogen and were cryosectioned at 20 μm. Sections were labeled with the TUNEL technique6 to identify the fragmentation of DNA characteristic of dying cells, after protocols published previously.9 Adjacent sections were labeled with a mouse monoclonal antibody against bovine basic FGF (Type I; Upstate Biotechnology, Lake Placid, NY), with mouse monoclonal antibodies to rod opsin (Rho4D2, a gift from Robert Molday, University of British Columbia, Vancouver, BC, Canada), with a rabbit polyclonal antibody raised against a peptide mapping at the carboxyl terminus of the human Flg (FGFR1) receptor (Santa Cruz Biotechnology Inc., Santa Cruz, CA); with a polyclonal...
antibody to ciliary neurotrophic factor (CNTF, cat AB 1499P; Chemicon International Inc., Temecula, CA), and/or with a polyclonal antibody to glial fibrillary acidic protein (GFAP; Dako, Carpinteria, CA). Protocols for the use of these have been published previously.1,10,11 To demonstrate the general cellular structure of the retina, many sections were also labeled with the DNA-specific dye bisbenzamide (Calbiochem, La Jolla, CA). Sections were incubated for 2 minutes at room temperature in a 1:10,000 dilution of bisbenzamide in 0.1 M PBS.

Quantifying TUNEL-Labeling, Layer Thickness
Counts of TUNEL+ profiles (apoptotic cells) were made using a calibrated 20X objective and an eyepiece graticule. Each section was scanned from the superior to inferior edge in 400-μm steps, and the number of TUNEL+ profiles was recorded for each 400-μm length of the section. Separate counts were recorded for the INL and ONL. Sections adjacent to those through the optic nerve head were used, to minimize variations in retinal length and position. Counts were averaged from at least two sections per animal.

Oxygen Measurements
Animal Preparation. Eleven P23H rats aged 15 to 29 weeks, and 11 SD control animals matched for age were used for intraretinal oxygen measurements. The rats were housed two per cage on sawdust. They were fed standard laboratory rat chow with water ad libitum. On the day of the experiment the rat was anesthetized with an intraperitoneal injection of 100 mg/kg 5-ethyl-5- (1’-methyl-propyl)-2-
thiobarbiturate (Inactin; Sigma-Aldrich, St. Louis, MO). Atropine sulfate (20 μg) was administered intramuscularly to minimize salivation. The trachea was cannulated for mechanical ventilation, the left internal jugular vein for venous infusion, and the femoral artery for continuous blood pressure monitoring and occasional aspiration of arterial blood (60 μL) for blood gas analysis (CIBA-Corning 238; Corning, NY). The rat was then mounted prone in a modified stereotaxic apparatus and the head fixed in position. The rat was artificially respired (rodent respirator, model 683; Harvard Apparatus, Holliston, MA) with a ventilation rate of 90 breaths per minute and a tidal volume appropriate to ensure normal arterial pCO₂ levels. Rectal temperature was monitored and maintained at 37.5°C by a homeothermic blanket (Harvard Apparatus). Experiments usually lasted 8 hours, after which the rat was killed with an anesthetic overdose.

**Ocular Surgery.** The left eye was used for all oxygen experiments. The pupil was dilated with 1% tropicamide (Mydriacyl; Alcon Laboratories, French’s Forest, NSW, Australia). The upper eyelid was partially removed, and an eye ring was sutured to the conjunctiva at the limbus and fixed to the stereotaxic framework. A small incision was made in the superior nasal quadrant with a diamond knife, just posterior to the limbus to allow entry of the microelectrode. Damage to the larger choroidal vessels or posterior lens capsule was avoided. A planoconcave contact lens was placed on the cornea to allow the vitreous and the fundus to be visualized with an operating microscope during all intraocular manipulations.

**Intraretinal Oxygen Profiles.** The microelectrode techniques were similar to those reported in our earlier publications. Recessed oxygen sensitive microelectrodes were manufactured and calibrated in our own laboratory. The microelectrode entered the eye through the entry hole, which was also the locus of rotation of our microsurgical system, such that rotation of the positioning system pivots the electrode about the entry point. The small size of the electrode tip (1 μm) coupled with electrode beveling techniques and the high acceleration piezoelectric translation of the electrode produced highly reproducible measurements of intraretinal oxygen distribution. Intraretinal oxygen profiles were measured in the inferior retina, approximately two to three disc diameters from the disc margin. The electrode tip was initially placed at the surface of the chosen area of retina under microscope observation. The electrode was stepped through the retina in 10-μm increments, under computer control, until a peak oxygen level within the choroid was reached. The measurement was repeated during stepwise withdrawal of the electrode. Although very close agreement between the insertion and withdrawal profiles was routinely achieved, the withdrawal profiles were used for data analysis, as they tended to be less influenced by artifacts associated with mechanical stress on the electrode tip during penetration. The oxygen tension measured by the microelectrode and systemic conditions such as arterial blood pressure, were recorded continuously on an eight-channel chart recorder (model LR81100; Yokogawa, Tokyo, Japan). The readings of each channel were also accessed every 2 seconds through a computer interface (GPIB-IEEE) and the data logged directly to a spreadsheet along with the relative position of the microelectrode. All microelectrode measurements were performed in photopic conditions.

**Statistics.** All average values for oxygen tension are stated as means ± SE. Significant differences were determined using Student’s t-test, with P < 0.05 accepted as significant. All statistical testing was performed on computer (SigmaStat; SPSS Science, Chicago, IL).

**Electroretinogram Recording**

Electrophysiological recordings were taken from four SD and four P23H-3 animals at P120. Animals were dark adapted overnight (minimum of 12 hours) and set up under dim red illumination. Anesthesia was achieved with intramuscular injections of ketamine (60 mg/kg) and xylazine (10 mg/kg; Lyppar; Castle Hill, NSW, Australia). Puppies were dilated with 1 drop of tropicamide (Mydriacyl 0.5%; Alcon Laboratories). Corneal hydration was maintained throughout the duration of recordings with synthetic tears (Viscoatears; Carborner 940 2 mg/g; CIBA Vision, Baulkham Hills, NSW, Australia), which also aided in maintaining electrical contact with the corneal electrode. Body temperature was maintained close to 37°C with an electric blanket controlled by feedback from a rectal temperature probe (Harvard Apparatus). The ERG was recorded between a Pt wire touching the cornea and an Ag/AgCl pellet (Clarke electrode E206; SDR Clinical Technology, Middle Cove, NSW, Australia) in the mouth.

The animal was positioned with the head approximately in the center of a 60-cm diameter Ganzfeld, with the flash source positioned centrally at approximately 45° above the animal’s head. A further 10 minutes of dark adaptation was allowed before commencement of recording. The flash stimulus was provided by a (model 70; Metz GmbH, Zirndorf, Germany) flash unit and flash intensity was attenuated over a 7-log-unit range with near-neutral density filters. To minimize the cone contribution to the ERG, all stimulus flashes were delivered through a filter (Wratten 47A; Kodak, Rochester, NY) in place. Stimuli were controlled, recorded, and displayed on a computer workstation (MacLab/200 system and Scope software; ADInstruments, Castle Hill, NSW, Australia). Responses were band-pass filtered at 0.3 to 500 Hz. A 50-Hz notch filter was used to minimize mains noise. With attenuations between 1.4 and 7.0 log units, two to three responses were averaged with an interstimulus interval of between 20 (neutral density [ND] 7.0) and 120 (ND 1.4) seconds. At the lowest attenuation (i.e., the brightest...
flash) a single response was recorded, after an interval of at least 2 minutes from any prior flash.

The flash source was calibrated at the CSIRO National Measurement Laboratory (Lane Cove, NSW, Australia), using a photometer (SD2; Hagner). Conversion from illuminance to irradiance units involved adjustment for the spectral distribution of the flash source (spectral curve provided by Metz), duration of the light pulse (4 ms), and transmission properties of the filter (Wratten-47; Eastman Kodak). The conversion from flash intensity at the cornea to photoisomerizations per rod per second was based on previously published methods, with modifications accounting for the efficiency of photon capture in rodent scotopic vision. The final estimate of flash output (with a Wratten 47 filter) in photoisomerizations per rod per second was 1.09 × 10^7. In practice, the brightest flash used was with attenuation by the 0.7 neutral density filter (Δ = 2.18 × 10^5). This was of sufficient intensity to elicit saturated a-wave responses.

The a-wave amplitude was measured from baseline to the a-wave trough and implicit time (latency) was measured to the trough peak. The b-wave amplitude was determined from a-wave trough to b-wave trough and implicit time (latency) was measured to the trough peak.

**RESULTS**

**Time Course of Photoreceptor Death in the P23H Rat**

At P5 in the P23H-3 retina, the neuroblast layer has not separated into the inner (INL) and outer (ONL) nuclear layer (Fig. 1); this separation is evident by P7. Until P10, TUNEL\(^+\) (dying) cells (red in Fig. 1) were found predominantly in the INL. The number of TUNEL\(^+\) cells in the INL decreased to near 0 by P23. TUNEL\(^+\) cells appeared in the ONL at approximately P10 and increased in number until P23 (Fig. 2A), after which the number declined. They persisted in the young adult (P105–P120), by which time the ONL was markedly thinner than in the SD adult control.

These trends are shown quantitatively in Figure 2. The decline in TUNEL\(^+\) profile frequency in the INL did not differ markedly between the P23H-3 and the SD control (data not shown). The time course of cell death in ONL (onset, peak, decline) matched the time course of photoreceptor death in the P23H-3 strain. However, the frequency of TUNEL\(^+\) cells in the ONL (Fig. 2A) was of similar manner of the rise, peak, and decline in TUNEL\(^+\) cells in the ONL was low (Fig. 2B). The thinning of the ONL in the P23H-3 strain has been clearly visible in these animals, presumably due to retinal thinning. The radial distribution of the retinal vessels was clearly seen (v, vein; a, artery). Intraretinal penetrations were made in regions of retina free of major retinal vessels. Scale bar: (A, B, D–G, I, J) 25 μm; (G) 10 μm. The scale bar in (D) applies to (B) and that in (G) applies to (H).

**Expression and Sites of Action of Stress-Inducible Factors**

In SD control rats, GFAP expression was confined to astrocytes at the inner surface of the retina (Fig. 3A, red). In the P23H-3 retina, GFAP expression was prominent also in the processes of Müller cells, which cross the retina radially (Fig. 3B). In SD control rats, FGF-2 was prominent only in Müller cells, which cross the retina radially (Fig. 3B). In the P23H-3 retina, labeled and analyzed as for (I), (K) Fundus photograph of a 15-week-old P23H rat with an oxygen-sensitive microelectrode (arrow) in position in the inferior retina. The choroidal vasculature was clearly visible in these animals, presumably due to retinal thinning. The radial distribution of the retinal vessels was clearly seen (v, vein; a, artery). Intraretinal penetrations were made in regions of retina free of major retinal vessels. Scale bar: (A, C, D–G, I, J) 25 μm; (G) 10 μm. The scale bar in (D) applies to (B) and that in (G) applies to (H).
INL (Figs. 3A, 3C) with some expression in ganglion cell cytoplasm and astrocyte nuclei (Fig. 3C; for a more detailed description see Ref. 3). In the P23H-3 retina FGF-2 expression was markedly upregulated, particularly in the ONL (Figs. 3B, 3D–G). At higher power (Figs. 3F, 3G) the FGF-2 was seen to concentrate in the cytoplasm of photoreceptor somas. In the SD control retina, CNTF was present in astrocytes at the inner surface and was detectable at low levels across all layers of the retina (Fig. 3C; for more detail see Ref. 3). In the P23H-3 retina, CNTF levels were upregulated in Müller cell processes crossing the retina (Figs. 3D, 3E). At higher magnification CNTF was apparent in the cytoplasm of Müller cells in the INL (Figs. 3F, 3H), at the OLM (Figs. 3F, 3G, arrows) and in the processes, which extend radially from the inner and outer poles of Müller cell somas in the INL (Fig. 3H).

In SD control rats, FGFR1 was present in the cytoplasm of photoreceptor somas in the ONL, whereas FGF-2 was prominent only in Müller cell somas in the INL (Fig. 3I, left). When areas of the image were selected where both red (FGFR1) and green (FGF-2) signals were high, these yellow pixels were found only in Müller cell somas (Fig. 3I, right, at top). In the P23H-3 retina FGF-2 was also prominent in the ONL, and the “yellow extraction” analysis highlighted photoreceptor somas in the ONL, as well as Müller cell somas. As argued previously, these yellow pixels suggest colocalization and binding of ligand and receptor. Thus, these images suggest that in the P23H-3 retina, there is an upregulation of FGF-2/FGFR1 binding in the cytoplasm of photoreceptor somas.

The Oxygen Status of the P23H Retina

Figure 3K is a fundus photograph from a 15-week-old P23H-3 rat, with an oxygen-sensing microelectrode with the tip positioned in the inferior retina. In these animals, the choroidal vessels were much more easily seen than in normal SD rats, a phenomenon presumably related to retinal thinning. Typical intraretinal oxygen profiles for a 17-week-old P23H-3 rat are shown in Figure 4B. Data for an age-matched SD control rat are shown in Figure 4A. In the control rat, the intraretinal oxygen distribution reflected the uptake of oxygen in both the inner and outer retina. This was evident in the rapid changes in oxygen gradient at ~170- and 330-μm track distances from the retinal surface. In the P23H rat the oxygen-consuming zone in the outer retina was much more evident, and the choroidal peak in oxygen tension was reached at a much reduced track distance, indicating retinal thinning.

When averaged profiles for the SD and P23H-3 rats (n = 11 for both groups) are superimposed (Fig. 5), it is apparent that the principal difference between the strains is that the oxygen consumption zone in the outer retina is absent from the P23H-3 data. Statistically, pO2 levels were not significantly different (P = 0.073) in the superficial retina, inner plexiform layer (P = 0.059), or the choroid (P = 0.613), but the average oxygen level was significantly higher (P = 0.018) in the outer retina of the P23H rats (26.70 ± 2.81 mm Hg) than in the control rats (18.71 ± 1.33 mm Hg). The average values of outer retinal oxygen tension were determined by averaging together every point in the outer retina in each animal. This overcame the problem of retinal thinning in the P23H rats and allowed a direct comparison of outer retinal oxygen level in the two groups.
the outer retina. Evidence that the retina is highly protected includes the binding of FGF-2 to its receptor FGFR1, which is believed to activate antiapoptotic pathways, and the deceleration of the rate of photoreceptor degeneration after it reaches its maximum in the juvenile.

**Hyperoxia in the Degenerating Retina**

Models of oxygen flow in the retina have been developed that relate retinal oxygen tension to oxygen consumption, over a wide range of conditions. When, as in the P23H-3 retina, the population of photoreceptors is depleted, these models assume a corresponding reduction in oxygen consumption by photoreceptors and predict an increase in oxygen tension in the outer retina. This increase goes largely uncompensated because the choriocapillaris autoregulates only poorly (reviewed in Refs. 2, 19). This prediction has now been confirmed in three models of retinal degeneration, the RCS rat, the Abyssinian cat (Linsenmeier RA, et al. IOVS 2000;41:ARVO Abstract 1268) and, in the present study, in the P23H-3 rat. It is intriguing that inner retinal oxygen levels and inner retinal oxygen metabolism are largely sustained after photoreceptor degeneration. This was found in the RCS rat even after almost complete degeneration of the outer retina. Contrasting results were found in the urethane model of retinal degeneration in which almost all inner retinal oxygen metabolism was lost after photoreceptor degeneration.

Less direct evidence that the photoreceptor-depleted retina is hyperoxic comes from observations on the status of retinal vessels. Hyperoxia is known to cause the constriction and obliteration of vessels, effects that are particularly marked in the retina because of the poor autoregulation of the choriocapillaris (reviewed in Refs. 19, 20). The mechanisms of vascular thinning relate to the regulation by oxygen of angiogenic factors. In the late stages of both human RP and rodent models, retinal vessels thin, suggesting hyperoxia of the inner retina. Further, it has been shown in the rodent models, though not yet in humans, that hypoxia reverses the depletion-induced thinning of retinal vessels.

**Toxicity of Hyperoxia in the Degenerating Retina**

The question arises (reviewed in Ref. 2) whether chronic outer retinal hyperoxia contributes to the stress to which the depleted retina appears subject. It is well known that lack of oxygen, or anoxia, is a common environmental challenge. However, there is evidence to demonstrate that oxidative stress may not only be caused by hypoxia or anoxia, but also by hyperoxia. Deviation of oxygen tension above or below normal physiological levels may dramatically change the intracellular redox equilibrium and may alter gene expression patterns in the manifestation of an adaptive stress response. The oxygen consumption of the retina on a per-gram basis has been described as higher than that of the brain. Since the brain consumes a highly disproportionate share of the total body’s oxygen uptake, the retina is one of the highest oxygen-consuming tissues in the body. Like the brain, the retina has low levels of the antioxidant enzyme catalase and is rich in iron, which can be a potent catalase for hydroxyl radical formation. These characteristics make the brain and retina particularly sensitive to oxidative stress. The roles of oxidative stress in neurodegenerative diseases such as retinal degeneration should not be underestimated.

In the rabbit, and mouse, hyperoxia has been shown to be directly and specifically toxic to photoreceptors. It is possible then that depletion-induced hyperoxia is a factor in making many retinal degenerations relentlessly progressive.

It is a clinical feature of human retinal degenerations that many begin with some specificity, affecting rods but not cones or vice versa, and then lose their specificity. This loss of specificity is

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**DISCUSSION**

The present results suggest that the adult P23H-3 retina is a valuable model of a photoreceptor-depleted retina functioning in a high-stress, high-protection environment. Evidence that the photoreceptor population is depleted is clear from the ERG. Evidence that the retina is under chronic stress includes the persisting degeneration of photoreceptors at higher than control rates, upregulation of stress-inducible proteins, and chronic hyperoxia in a high-stress, high-protection environment. Evidence that the choriocapillaris autoregulates only poorly (reviewed in Refs. 2, 19). This prediction has now been confirmed in three models of retinal degeneration, the RCS rat, the Abyssinian cat (Linsenmeier RA, et al. IOVS 2000;41:ARVO Abstract 1268) and, in the present study, in the P23H-3 rat. It is intriguing that inner retinal oxygen levels and inner retinal oxygen metabolism are largely sustained after photoreceptor degeneration. This was found in the RCS rat even after almost complete degeneration of the outer retina. Contrasting results were found in the urethane model of retinal degeneration in which almost all inner retinal oxygen metabolism was lost after photoreceptor degeneration.

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**Electroretinogram**

Figures 6A and 6B show an intensity–amplitude series for SD and P23H-3 adult retinas. Both are from the dark-adapted retina. The P23H-3 a-waves appear normal in time course but reduced in amplitude. Over a wide range of intensities, the amplitude of the P23H-3 a-wave was approximately 60% of the SD a-wave (Fig. 6C, n = 4 for both SD and P23H-3 groups). The amplitude difference was significant (P < 0.01 on a two-tailed t-test) at attenuations from 0.7 to 4.0 log units—thus, more than a 20,000-fold range of stimulus intensity.

**FIGURE 6.** Electroretinogram of young adult P23H-3 and SD rats, in dark-adapted conditions, shown as an intensity series from (A) a control SD rat and (B) an age-matched P23H-3 rat. (C) Summary of a-wave amplitude as a function of intensity, for the two strains. Error bars, ±1 SD.
common, even in degenerations caused by mutations specific to rods, such as the rhodopsin mutations. Depletion-induced hyperoxia could be a factor in this loss of specificity. If confirmed, this would suggest that oxygen management could provide some reduction of stress to depleted retinas, which might slow the rate of progression of the degeneration.

Factors Determining Photoreceptor Death Rates in the Degenerating Retina

The present suggestion that depletion-induced hyperoxia of the ONL makes the late stages of photoreceptor degeneration both progressive and nonspecific also predicts that degenerations should accelerate, because oxygen levels increase as depletion progresses, and then should stop suddenly, when the population of photoreceptors is exhausted. Empirically, by contrast, many degenerations slow with age and continue through adult life, as reported herein and previously in the P23H transgenic rat. This deceleration may result from the upregulation of protective mechanisms (such as the protective factors FGF-2 and CNTF) by oxidative stress. The rate of photoreceptor death occurring in any retina is presumably determined not simply by the levels of stress experienced, but is the net outcome of the lethal effects of stress and the protective effects of the retina’s defense mechanisms.

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References


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