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THE CONTRAST SENSITIVITY OF CAT RETINAL GANGLION CELLS AT REDUCED OXYGEN TENSIONS

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SUMMARY

1. These experiments were done to investigate the effect of various degrees of hypoxia on the function of retinal ganglion cells (recorded in the optic tract) and on retinal oxygen tension.

2. The contrast sensitivity of the centre of X and Y cells, the surround of X cells and the non-linear subunits of Y cells were measured separately by choosing appropriate spatial and temporal parameters of a sinusoidal grating pattern.

3. Retinal oxygen tension was measured with a bipolar polarographic oxygen electrode positioned in the vitreous humor close to the retina.

4. The time course of changes in ganglion cell sensitivity and retinal oxygen tension was similar. However, oxygen tension frequently overshot the prehypoxic value at the end of hypoxia, while sensitivity did not.

5. The cat retina was rather resistant to hypoxia. Contrast sensitivity and mean firing rate did not change provided the arterial oxygen tension was above about 35 mmHg, but usually dropped precipitously at lower arterial values.

6. The apparent reason for this resistance is that retinal oxygen tension was well regulated, falling only 0·14 mmHg per mmHg of arterial oxygen tension for arterial values above about 35 mmHg, which corresponds to a retinal oxygen tension of about 10 mmHg. Retinal oxygen tension decreased more sharply (0·62 mmHg per mmHg) at lower values of arterial oxygen tension, where sensitivity also decreased.

7. The centre, surround and subunits reacted similarly to hypoxia. This suggests that lateral pathways (i.e. surround) and pathways which might be expected to use more synapses than the centre (i.e. surround and subunits) are not more susceptible to hypoxia.

INTRODUCTION

A reduction in the supply of oxygen to the visual system leads to impairments in many indices of visual function. Hypoxia reduces both absolute and increment sensitivity in humans (e.g. McFarland, Halperin & Niven, 1944; Ernest & Krill, 1971), decreases the amplitude of massed potentials in animals and humans (e.g.

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Granit, 1933; Noell, 1951; Bos, 1968; Brown, Hill & Burke, 1957; Massopust, Wolin & Barnes, 1966), decreases the responsiveness of single visual neurones (e.g. Bornschein, 1958; Drujan, Svaetichin & Negishi, 1971) and leads to structural changes in the retina (e.g. Webster & Ames, 1965).

Unfortunately, previous studies have not determined the magnitude of the change in oxygen tension which is required to cause a change in the function of visual cells. There are two reasons for this. First, in most of the earlier work anoxia or complete ischaemia was the only experimental condition, so the behaviour of visual cells under milder degrees of oxygen deprivation has remained unclear. Secondly, in those few studies which have investigated the effects of mild hypoxia, only the oxygenation of the blood has been measured and this is not necessarily a good indicator of tissue oxygen tension. In the present study recordings were made from retinal ganglion cell axons under various degrees of oxygen deprivation, and an intraocular, bipolar oxygen electrode was used to measure retinal oxygen tension. With these techniques it was possible to determine the dependence of retinal function on the local oxygen supply.

A further limitation of previous studies is that they have dealt only with changes in the response of visual cells to a fixed stimulus, usually a strong one. Studying changes in the sensitivity of cells was considered to be preferable here, because this measure is less dependent on non-linearities in the stimulus–response relationship of the cells and because it is more comparable to psychophysical measures.

The major finding of this study is that both the contrast sensitivity of retinal ganglion cells and the oxygen tension of the inner retina are maintained at nearly normal levels provided that the arterial oxygen tension is above about 35 mmHg, while below that both retinal oxygen tension and ganglion cell sensitivity frequently drop sharply. This suggests that the autoregulation of retinal oxygen tension is essential for the maintenance of normal retinal function. Portions of the work have been presented at the Society for Neuroscience Annual Meeting, 1977, and at the Spring Meeting of the Association for Research in Vision and Ophthalmology, 1979.

METHODS

Preparation. Thirty-one adult cats were used, nineteen for ganglion cell recordings alone, seven for measurements of retinal oxygen tension alone and five for both types of measurements. The animals were given 0·2 mg of atropine subcutaneously and then anaesthetized with halothane (Fluothane) in oxygen. Once a saphenous vein had been cannulated the rest of the surgery was done under sodium thiamylal (Surital) anaesthesia. The spine was elevated to help prevent atelectasis of the lungs. A controlled heating pad maintained the animal's temperature at 37–38 °C. The head was mounted stereotaxically and a hole was trephined in the skull above the right optic tract. The experiments were done with the animal under urethane anaesthesia. A dose of 200 mg/kg was given during surgery, followed by 20–30 mg/kg per hr during the experiment. Dexamethasone (Decadron-LA, 4 mg I.M.) was given to help control inflammatory reactions and cerebral oedema. Topical phenylephrine (Neosynephrine) and atropine were applied to retract the nictitating membranes and dilate the pupils. The eyes were fitted with contact lenses of appropriate dioptric power with artificial pupils (4–5 mm diameter). To ensure ocular stability cats were paralysed with gallamine triethiodide (Flaxedil, 20–50 mg/kg per hr), mixed in some cases with Ambex, a nutrient solution containing 5% glucose as well as amino acids. During paralysis the animal was respirated with a Harvard small animal respirator via a tracheotomy tube.

The animal's heart rate, mean femoral arterial blood pressure, and end-tidal CO_2 were monitored continuously. The heart rate was typically in the range of 160–200/min and changed little with hypoxia. The blood pressure was recorded with a Harvard apparatus pressure transducer and was typically 100–150 mmHg before hypoxia. The blood pressure usually increased at the beginning of hypoxia. Breathing 10% oxygen caused a mean increase of 26 mmHg and breathing 5% oxygen caused a mean increase of 37·5 mmHg. During more severe hypoxia the blood pressure sometimes fell after this initial increase, dictating that hypoxia be ended to avoid permanent damage to the animal.

The end-tidal CO_2 was measured with a Beckman LB1 Medical Gas Analyser. Awake cats have an arterial carbon dioxide tension of 30 mmHg (about 4% end-tidal) and a pH of 7·4 (Herbert & Mitchell, 1971; Lahiri, 1975). When our experiments were done we were unaware of this, so the stroke rate and volume of the respirator were adjusted to maintain end-tidal CO_2 in the range of 4·5–5%. The cats might then have been expected to be acidotic, but the arterial pH, measured with a Radiometer PHM 71 Acid-Base Analyser, was in the normal range of 7·35 to 7·45. Changes in CO_2 and pH were generally small during hypoxia.

Recording of single action potentials and visual stimulation. Lacquer- or glass-coated tungsten electrodes (Hubel, 1957; Levick, 1972) were placed in the optic tract to record ganglion cell spikes. Standard pulses triggered by each spike were collected into peristimulus time histograms.

The visual stimuli were sinusoidal gratings generated on an oscilloscope (Tektronix 7603, P31 phosphor) 9·1 deg in diameter in the earlier experiments and 16 by 13 deg in later ones. The mean luminance (L_0) was varied by using neutral density filters and was in the range of 16–0·06 cd/m^2. The contrast, $C = (L_{max}-L_{min})/(L_{max}+L_{min})$, spatial frequency and temporal modulation were controlled by a PDP-11/10 computer. Three types of temporal modulation were used. First, the sensitivities of the centre and surround were studied with a grating drifting across the receptive field so that the luminance of each point was modulated at 1·5–2 c/sec (a 'drift frequency' of 1·5–2 c/sec). Secondly, a stationary grating with sinusoidal contrast reversal at 1 or 2 Hz was used to measure the sensitivity of the non-linear subunits of Y cells (Hochstein & Shapley, 1976*a*, *b*). Finally a stationary grating whose contrast reversed suddenly at 1 Hz was used to classify X and Y cells (Enroth-Cugell & Robson, 1966).

Sensitivity tracking. X and Y cells respond to drifting gratings with a modulation of the firing rate whose fundamental Fourier component is at the drift frequency of the grating. The *response* of a cell was taken to be twice the amplitude of this fundamental component measured from peristimulus time histograms as described by Hochstein & Shapley (1976*a*) and Linsenmeier & Jakiela (1979). For a histogram with no harmonic distortion, twice the fundamental corresponds to the peak-to-trough response amplitude. The distortion in histograms collected before hypoxia was relatively small; when the amplitude of the fundamental was about 10 spikes/sec the average amplitudes of the second and third harmonics were both about 2·5 spikes/sec in Y cells and 1·5 spikes/sec in X cells. However, during hypoxia a fall in the mean rate of discharge sometimes introduced more distortion. This is considered further in the Results (p. 65).

Contrast sensitivity is defined here as the reciprocal of the contrast needed to evoke a criterion response and implies the ratio of response to contrast. Contrast sensitivity was determined repeatedly using the computer in the following way. The experimenter chose the spatial frequency and the initial contrast of the grating, which then drifted until a predetermined number of cycles of the grating (16–32) had crossed a point in the receptive field. The size of the fundamental component in the peristimulus time histogram was then calculated. If the peak-to-trough response was within 10% of the criterion response of 20 spikes/sec, the contrast was left unchanged and the next histogram was collected. If the actual response was more than 10% larger or smaller than the criterion response, the computer changed the contrast of the grating before collecting another histogram. Cycles of collecting a histogram, measuring the response and adjusting the contrast each took about 20 sec, and continued until stopped by the experimenter. Because the responses in successive histograms bracketed the criterion value, it was possible to estimate contrast sensitivity from a few histograms and to track sensitivity changes over time.

Centre, surround and subunit sensitivity. By choosing appropriate spatial and temporal parameters of the grating it was possible to study selectively the effect of hypoxia on the centre or surround of X cells and the centre or subunits of Y cells. The choices were based on the following considerations. For X cells Enroth-Cugell & Robson (1966) found that the contrast sensitivity, S,

as a function of spatial frequency, ν, could be fitted well by assuming that the receptive field was composed of two antagonistic mechanisms, each with a Gaussian weighting function:

$$S(\nu) = S_c(\nu) - S_s(\nu) = \pi K_c r_c^2 \{\exp[-(\pi r_c \nu)^2]\} - \pi K_s r_s^2 \{\exp[-(\pi r_s \nu)^2]\} \quad (1)$$

Here K_c and K_s are the maximum sensitivities of the centre and surround and r_c and r_s are characteristic radii of the centre and surround. (Enroth-Cugell & Robson's parameter K which multiplied both terms has been incorporated into K_c and K_s.) By taking the ratio of the centre to the surround term (S_c/S_s) in eqn. (1), and using data from Table 1 and Fig. 9 of Enroth-Cugell & Robson (1966) it can be shown that the centre is at least 100 times more sensitive than the surround to spatial frequencies at or above the peak of the contrast sensitivity curve. This has been confirmed on our own X cell sample and we find that in Y cells the centre also dominates strongly at high spatial frequencies. Practically, this means that by using a drifting grating of high spatial frequency one can study the centre in isolation, and this approach was taken in the experiments described in the first part of the Results.

For spatial frequencies below the peak of the contrast sensitivity curve S_c/S_s decreases but is always greater than unity. While no single spatial frequency can be used to measure the surround sensitivity, it can be estimated by combining information from low and high spatial frequencies. Experiments based on this method are described in the second section of the Results. In addition to the centre and surround, Y cells have non-linear components in their receptive fields which have been called subunits, and which can be studied in isolation by using a stationary grating of high spatial frequency whose contrast reverses sinusoidally (Hochstein & Shapley, 1976*a*, *b*). The response to this stimulus is at the second harmonic of the contrast reversal, and can be obtained at a higher spatial frequency than the response to drifting gratings (see Fig. 8*A*), so it cannot be contaminated by the response of the centre. The sensitivity to this stimulus can be tracked in the same way as the sensitivity to a drifting grating, and experiments using this stimulus are also described in the second section of the Results.

Eye movements. Gratings were chosen as stimuli in these experiments partly because slow eye movements occur during hypoxia, even with large doses of Flaxedil (Linsenmeier & Hertz, 1979). Eye movements could displace a spot stimulus to a less sensitive part of the receptive field, leading to sensitivity changes unrelated to hypoxia. However, if one uses stimuli which are large, and for which the spatial phase of the stimulus with respect to the receptive field is unimportant (such as drifting gratings, or, for Y cells, contrast reversal gratings of high spatial frequency), it is only necessary that eye movements be small during the 8–16 sec required for the accumulation of each peristimulus time histogram.

Oxygen measurements. Intermittent measurements of arterial oxygen tension were made on blood samples with a Radiometer PHM 71 Acid-Base Analyser equipped with an oxygen electrode. The arterial oxygen tension before hypoxia was usually 90–100 mmHg.

Measurements of retinal oxygen tension were made with bipolar polarographic oxygen electrodes (Clark-type, Clark (1956)) shown in Fig. 1.

Details of the construction of the membrane and electrode can be found in Goldstick, Fry, Caprini, Wagner & Ellwein (1973) and Gutherman (1977). Electrodes were polarized at 0·8 V. Each electrode was calibrated in saline solutions at 37 °C equilibrated with 0, 5, 10 and 21 % O_2 just before insertion into the eye and was recalibrated after being withdrawn from the eye. The electrode current was linear with the oxygen tension of the solution, and the current corresponding to a given oxygen tension drifted less than 3 % per hr. The time constant for the response of these electrodes to a step change in oxygen tension was 3–7 sec. For measurements of retinal oxygen tension the sclera of the left eye was exposed and a hole was made in the eye a few millimetres posterior to the limbus near the horizontal meridian. An oxygen electrode was inserted through a trocar in this hole and was advanced through the vitreous humor until a change in the amount of light reflected from the tapetum indicated that the electrode had just barely dimpled the retina. The electrode was then withdrawn 100–200 μm. Usually the electrode was placed about two disk diameters above the optic disk. Electrode current was measured with a Keithley 414S Picoammeter and chart recorder.

The intraocular pressure was measured in three animals by inserting a needle in the anterior chamber. Upon making the hole in the eye for the electrode the intraocular pressure dropped from about 15 to about 5 mmHg and did not recover over 2–3 hr. Little fluid leaked out of the eye, however, and the shape of the cornea was well maintained. This approximates the situation

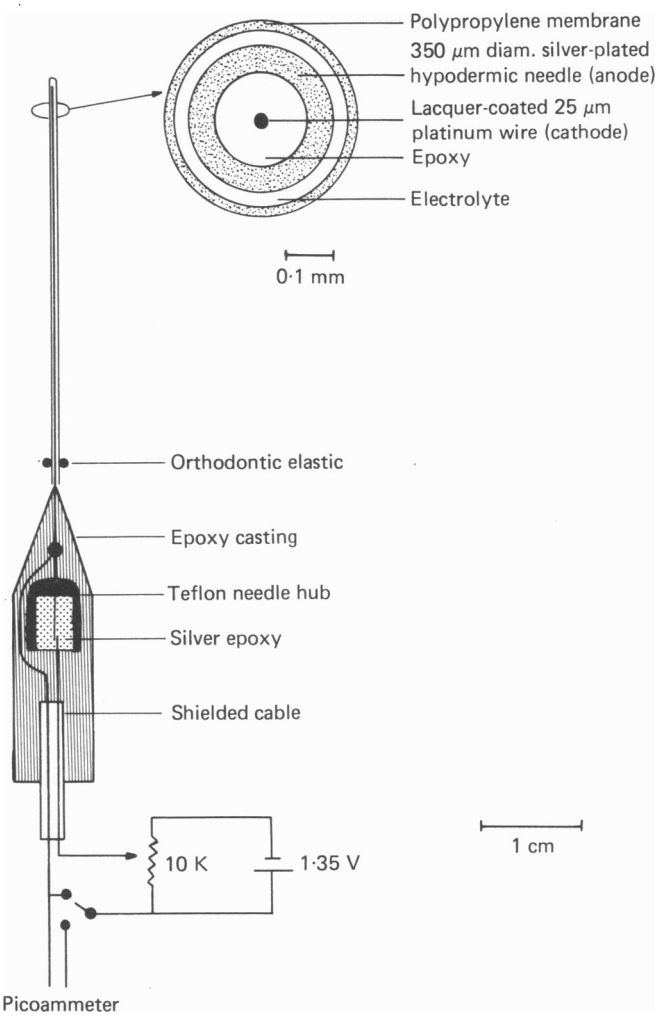

Fig. 1. Oxygen electrode used for measurements of oxygen tension in the vitreous humor near the retina (P_{vr,O_2}). The electrolyte was an isotonic gel with neutral pH. The polypropylene membrane was 13 μm thick. The sensitivity of the electrode was 10–20 pA/mmHg.

during recordings of oxygen tension, because no method was found to seal the opening without disturbing the membrane on the electrode.

RESULTS

The aim of this study was to correlate the type and extent of ganglion cell dysfunction with the magnitude of retinal hypoxia. Ideally, therefore, ganglion cell activity and retinal oxygen tension should always have been measured in the same animal. Simultaneous measurements were sometimes made, but they were difficult because (1) the preparation needed to do both kinds of experiments was more complicated, (2) the position of the oxygen electrode could not be checked while ganglion cell sensitivity was being measured and (3) the oxygen measuring system

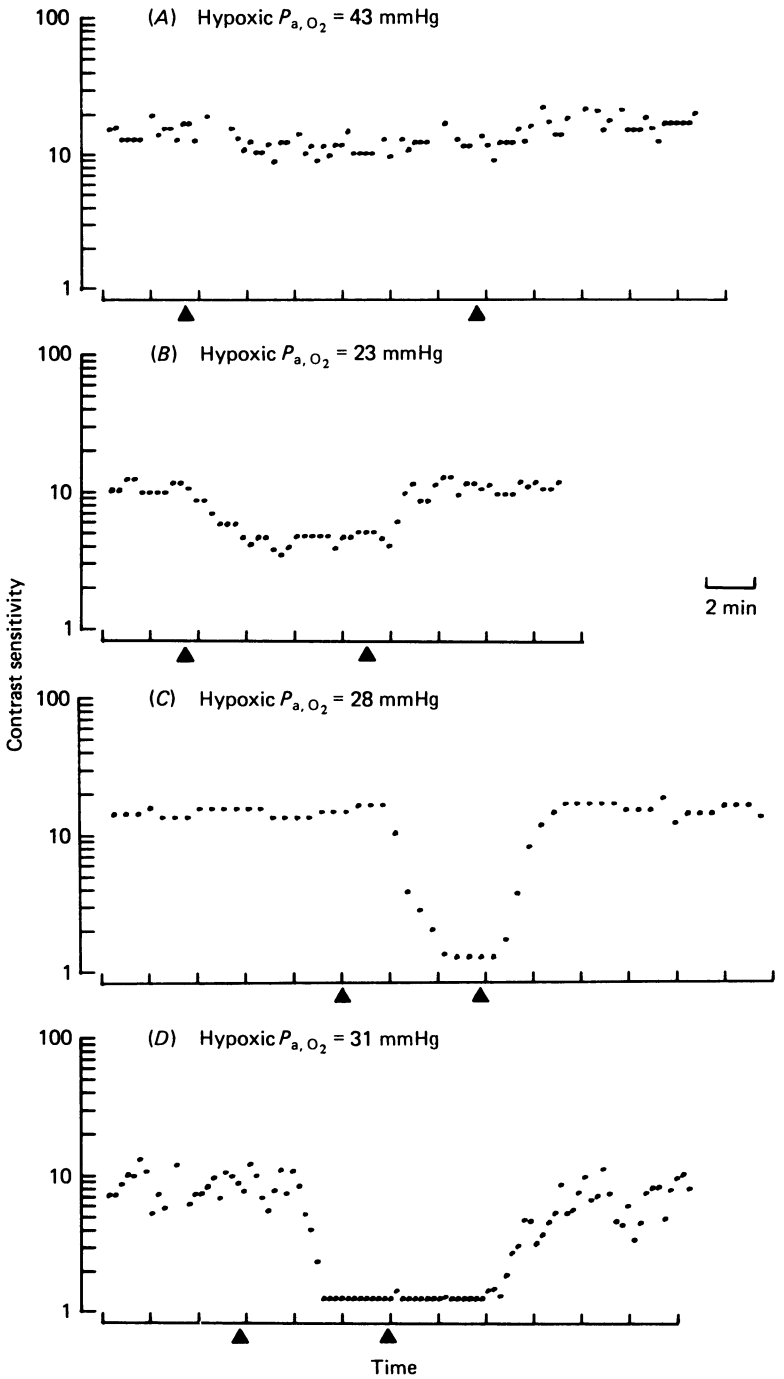

Fig. 2. Contrast sensitivity for the centre of four ganglion cells as a function of time during hypoxia. The animal was made hypoxic by changing the inspired gas between the arrows. Each point is the reciprocal of the contrast used during the accumulation of one histogram. In each case tracking was done at a spatial frequency above that at which the contrast sensitivity began to decline. The cell type, spatial frequency of the

introduced small spurious currents which made spike recording difficult when the signal-to-noise ratio was bad. This last problem was encountered only during hypoxia, when the spike amplitude often shrank, probably because changes in blood pressure caused movements of the brain relative to the fixed electrode.

The results are divided into three sections, The first demonstrates the dependence of ganglion cell centre sensitivity on arterial oxygen tension, and the second extends these findings to the surround of X cells and the subunits of Y cells. The third section establishes the relationship between retinal and arterial oxygen tension, extending the work of Alm & Bill (1972) to lower arterial values. These experiments taken together allow us to relate some aspects of retinal function to the local oxygen tension.

Ganglion cell centre sensitivity during hypoxia

The centre of ganglion cells proved very resistant to hypoxia, maintaining normal sensitivity until the arterial oxygen tension was 35 mmHg or less. The procedure was to determine the type of each cell (on- or off-centre, X or Y), and then, by using the sensitivity tracking algorithm described in the Methods, to measure its contrast sensitivity to gratings of several spatial frequencies drifting at 2 c/sec. Finally, sensitivity was tracked before, during and after hypoxia at a spatial frequency above the peak of the contrast sensitivity curve, usually one for which the contrast sensitivity was about 10 before hypoxia. Examples of sensitivity tracking during hypoxia are shown in Fig. 2.

The value of the ordinate of each point in Fig. 2 is the reciprocal of the contrast used during the accumulation of one histogram and provides an estimate of contrast sensitivity. Several features are apparent from these plots. First, before and after hypoxia the contrast sensitivity was stable. Secondly, the drop in sensitivity at the beginning of hypoxia usually took longer than the recovery of sensitivity at the end of hypoxia. Fig. 2*D* illustrates one of the rare exceptions. Thirdly, the recovery from even severe hypoxia was complete for the durations of hypoxia studied.

Contrast sensitivity changes were often so large that they could not be accurately measured. The maximum contrast available was 0·8, but during severe hypoxia even this was frequently insufficient to elicit the criterion response. Sensitivity changes were not always large, however, as shown in Fig. 2*A*, *B*.

A feature which is not apparent from Fig. 2 is that whenever the sensitivity during hypoxia was less than about $\frac{1}{3}$ of that before hypoxia the histograms were clipped; that is, the firing rate was zero over part of the stimulus cycle. Clipping is illustrated in Fig. 3 for the cell of Fig. 2*C*. When the firing pattern is distorted in this way the

grating, and mean luminance of the grating respectively were *A*, on-centre Y (36/1), 1·0 c/deg, 0·06 cd/m²; *B*, on-centre X (50/11), 0·8 c/deg, 12 cd/m²; *C*, on-centre Y (36/2), 0·125 c/deg, 0·06 cd/m²; *D*, on-centre Y (41/5), 0·5 c/deg, 0·6 cd/m². The high frequency fall-off of the contrast sensitivity curve began at: *A*, 0·75 c/deg; *B*, 0·5 c/deg; *C*, < 0·125 c/deg; *D*, < 0·5 c/deg. These values are not known with more precision because only a few points were obtained on the contrast sensitivity curves. Cells were usually studied at only one mean luminance, but the mean luminance appeared to have no effect on the reaction to hypoxia in those cells studied at more than one mean. In *C* and *D* there appears to be a steady state during hypoxia at a contrast sensitivity of 1·25, corresponding to the maximum contrast available, 0·8, but this was sometimes insufficient to elicit the criterion response.

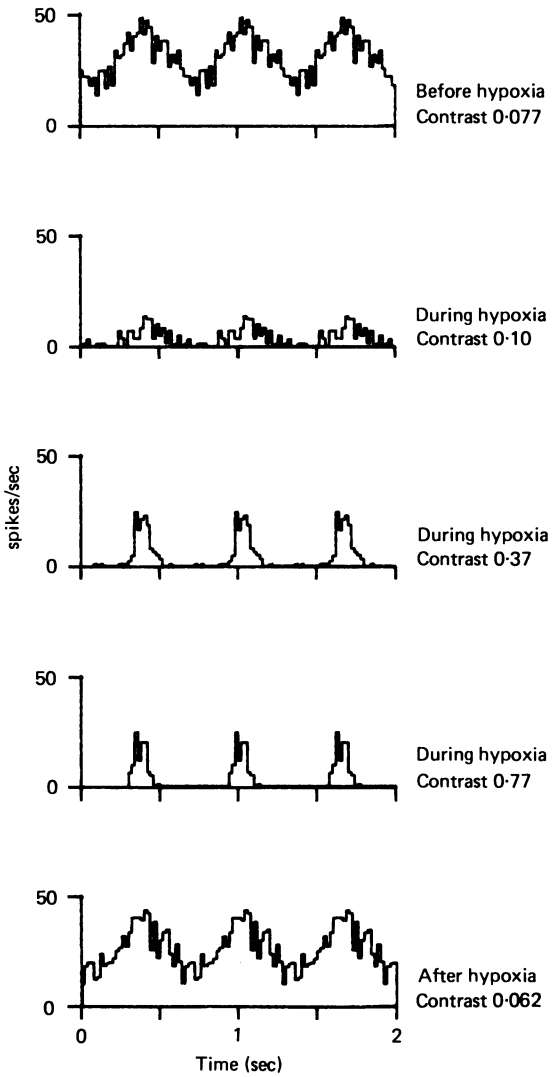

Fig. 3. Clipping of the firing rate during hypoxia for the cell of Fig. 2*C*. Drift frequency 1·5 Hz; spatial frequency 0·125 c/deg. Each histogram is the response of the cell to 32 cycles of the grating drifting past a point in the receptive field. Each histogram has been written out three times. The bin width was 10 msec, so 32 impulses/bin = 100 spikes/sec.

fundamental Fourier component no longer approximates the peak-to-trough difference in firing rate. However, clipping occurred only with large changes in sensitivity, and any response measure would then have given similar results. Another complication caused by clipping is that the modulation of firing rate no longer reflects the modulation of ganglion cell membrane potential. Therefore, a decrease in contrast sensitivity could be caused not only by a change in the input–output relation between receptors and the ganglion cell's spike generating mechanism, but also by (1) an increase in the ganglion cell's threshold for spike generation or (2) a hyperpolarizing shift in the resting potential.

Data like those shown in Fig. 2 were collected for fifty-two cells. The ratio of the sensitivity during hypoxia to that before hypoxia is plotted against the arterial oxygen tension in Fig. 4. The rather striking result is that when arterial oxygen tension was greater than 35 mmHg the sensitivity hardly ever changed. Below this

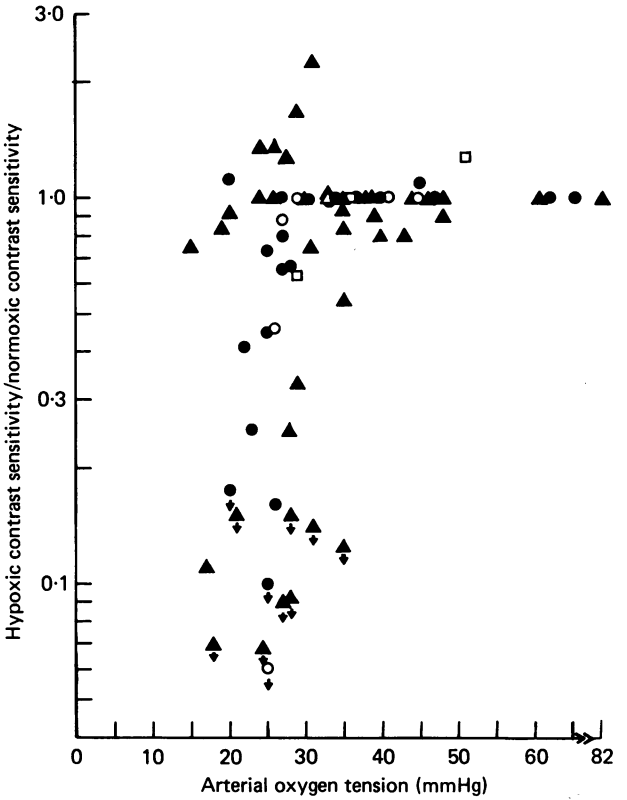

Fig. 4. Effect of hypoxia on the centre of fifty-two ganglion cells (seventy-two episodes of hypoxia). The ordinate is the ratio of the contrast sensitivity during hypoxia to that before hypoxia obtained from plots like those shown in Fig. 2. Descending arrows indicate cases for which the sensitivity change was larger than could be measured (i.e. the contrast required for the criterion response during hypoxia was larger than 0·8). Circles, X cells; triangles, Y cells; squares, unidentified. Filled symbols, on-centre; open symbols, off-centre cells. Thirty-one of these cells are also represented in Fig. 7 or 9. For seventeen of those cells more than one level of hypoxia was studied before returning the animal to room air, but in this Figure only the first level studied is represented. This has been done only in the interest of consistency; a plot of all the data looks nearly the same.

the sensitivity usually changed. The choice of a semilog plot of the ratio of sensitivities is somewhat arbitrary, and any method of plotting these data (e.g. contrast required during hypoxia minus contrast required before hypoxia) looked much the same. A semilog plot emphasizes the larger changes, which were in fact so large that they were unmeasurable, while minimizing the smaller ones, such as that shown in Fig. 2*A*.

The duration of hypoxia varied from 4 to 42 min, with a mean of 12·6 min. It is

natural to wonder whether the duration of hypoxia had any effect on the magnitude of the sensitivity changes shown in Fig. 4. One might expect sensitivity to change more for longer periods of hypoxia as well as for lower values of arterial oxygen tension. Unfortunately, this is a difficult hypothesis to test, because duration and arterial oxygen tension were not independent of each other, the duration being

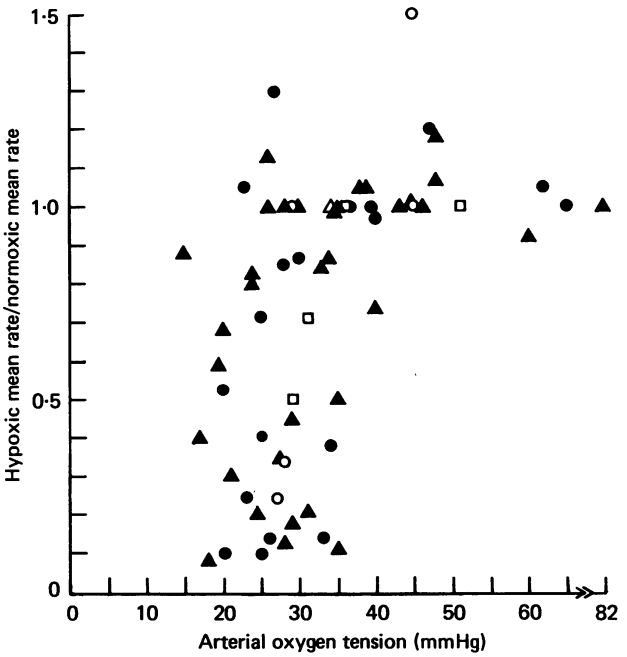

Fig. 5. Effect of hypoxia on the mean rate of firing (in the presence of continuous stimulation by the grating) for the cells of Fig. 4. Data from five cells have been deleted because of instabilities in the mean rate. As in Fig. 4, if more than one level of hypoxia was studied before returning the animal to room air, only the first level is represented here.

shorter when hypoxia was more severe (and consequently when the sensitivity changes were larger). Fig. 2 provides some evidence that the duration was not too important. Sensitivity did not change continuously but reached a steady state relatively quickly. The only exceptions occurred during three cases of severe hypoxia (arterial oxygen tension 15–25 mmHg for more than 12 min) when gradual decreases in blood pressure were accompanied by sensitivity changes beyond those seen at the beginning of hypoxia.

For nine cells in Fig. 4 sensitivity increased during hypoxia. For the cell with the largest elevation, the higher sensitivity was maintained for 8 min of hypoxia, and returned to the prehypoxic level following hypoxia. Others have found increases in the amplitudes of the e.r.g. (Bos, 1968) and evoked potentials in the optic nerve (Kayama, 1974), but most cells in this study did not show even transient increases in sensitivity.

For a few cells, sensitivity did not change even at an arterial oxygen tension below 30 mmHg. The apparent resistance of these cells may be explained by the variability

in average retinal oxygen tension at low values of arterial oxygen tension (see Fig. 11), or perhaps by the proximity of certain cells to blood vessels. Another possibility, suggested by the psychophysical data of Ernest & Krill (1971), is that resistant cells were located in a more central part of the retina. Unfortunately the positions of the optic disks were not always plotted, so the eccentricity of some cells could not be determined precisely. However, two X cells which were studied consecutively reacted quite differently to hypoxia. The first, at an eccentricity of 17 deg, had a sensitivity of only 10% of control at an arterial oxygen tension of 25 mmHg; the second, at an eccentricity of 6 deg had a normal sensitivity at an arterial oxygen tension of 27 mmHg. Another cell at an eccentricity of 5 deg was also quite resistant to hypoxia, having a sensitivity of 75% of control at 15 mmHg and 85% of control at 19 mmHg.

The effect of hypoxia on the mean rate of firing was similar to the effect on sensitivity. Fig. 5 shows that hypoxia had little effect until arterial oxygen tension was less than about 35 mmHg. Points near 0·1 represent cells which had very low mean rates during hypoxia, in the order of 5 spikes/sec. The mean in most cases returned to normal soon after hypoxia.

Rodieck & Smith (1966) described slow spontaneous rhythms in the firing rate of ganglion cells, which may sometimes be due to a deterioration in an animal's condition (Barlow & Levick, 1969). Hypoxia never induced rhythmicity in the firing rate, but on the occasions when these rhythms were observed hypoxia was able to modify their period.

Surround and subunits during hypoxia

Although we found the receptive field centre of X and Y type retinal ganglion cells to be rather resistant to hypoxia, it seemed possible that functional pathways other than those of the centre would be more susceptible, and that one might obtain an incorrect perspective on the over-all effect of hypoxia by considering only the receptive field centre. This section compares the effects of hypoxia on the surround of X cells and the non-linear subunits of Y cells to the effects of hypoxia on the centre. In general the centre and surround of X cells and the centre and subunits of Y cells all reacted similarly to hypoxia, but, because the stimuli were different for the two types of cells, they are discussed separately below.

X cells. As pointed out in Methods no single spatial frequency can be used to estimate the surround sensitivity alone, but one can obtain information about the surround by combining data from high and low spatial frequencies. If, for instance, the sensitivity to a high spatial frequency were unchanged during hypoxia, while the sensitivity to a low spatial frequency increased, one could conclude that the surround had become less sensitive while the centre remained unchanged. This example is a special case, however, and since hypoxia could cause several possible combinations of changes in sensitivity at two spatial frequencies it is desirable to put the analysis on a more general footing.

Before hypoxia a cell's contrast sensitivity can be described by eqn. (1). During hypoxia the sensitivities of the centre (S_c) and surround (S_s) are assumed to change by the factors F_c and F_s, resulting in a change in sensitivity $F(\nu)$ at ν:

$$F(\nu)S(\nu) = F_c S_c(\nu) - F_s S_s(\nu) \qquad (2)$$

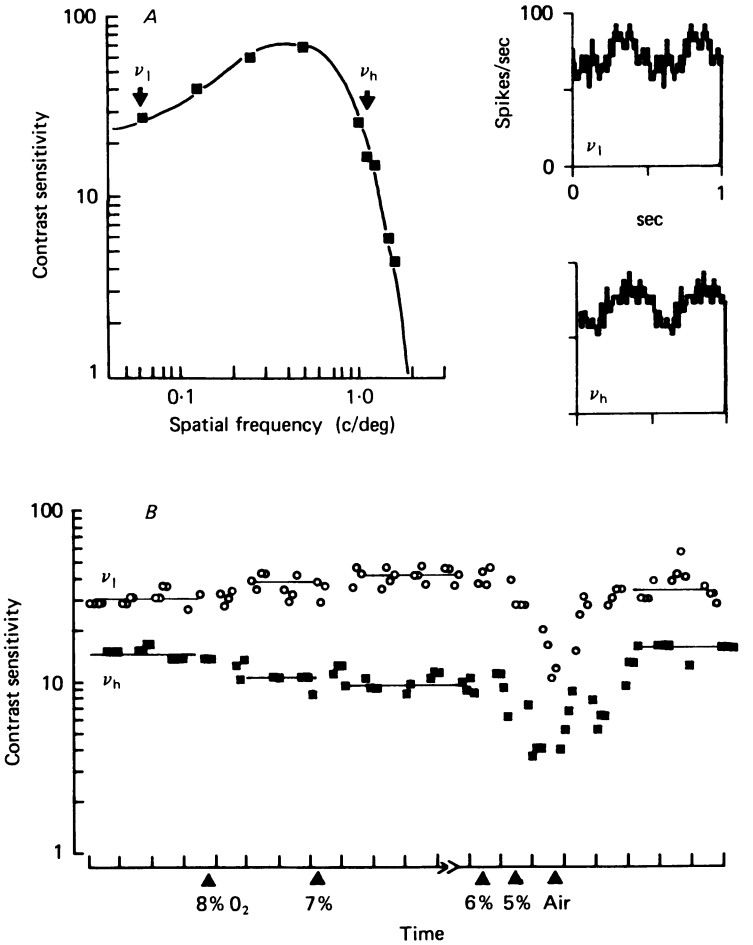

Fig. 6. *A*, contrast sensitivity of an on-centre X cell to drifting gratings. The ordinate is the reciprocal of the contrast required for a criterion response of 20 spikes/sec peak-to-trough. The line is a visual fit of the data to eqn. (1) with $r_c = 0{\cdot}36°$; $r_s = 1{\cdot}2°$; $K_c = 240$ and $K_s = 16$. On the right are histograms showing the criterion response at the two spatial frequencies at which sensitivity was measured during hypoxia, ν_l and ν_h. Twenty cycles drifted across the receptive field at 2 c/sec for these histograms. The bin width was 10 msec, so 20 impulses/bin = 100 spikes/sec. (Histograms have been written out twice.) *B*, contrast sensitivity as a function of time during hypoxia. The inspired gas was changed as indicated on the abcissa. Each division on the abcissa denotes 2 min, and the break shows where the sensitivity to a uniform field was measured for 4 min. Filled squares represent the sensitivity at ν_h and open circles are the sensitivity at ν_l. The P_{a,O_2} was 28 mmHg on 8 % O_2 and 25 mmHg on 7 % O_2. Points for which the response was more than 40 % away from the criterion value have been omitted because these do not give a good estimate of sensitivity. Horizontal lines give the average sensitivity over an interval of time.

F_c and F_s are assumed to be independent of spatial frequency, which is the same as assuming that K_c and K_s, but not r_c and r_s, change in hypoxia. This is discussed below (p. 72). To evaluate the relative effects of hypoxia on the centre and surround, one would like to know F_c and F_s, but in general one actually measures $F(\nu)$. F_c is easily determined, because it is the same as $F(\nu_h)$, the change in sensitivity at a

spatial frequency (ν_h) high enough that the surround contribution is negligible. F_s is estimated by also measuring the change in sensitivity at a low spatial frequency $F(\nu_l)$, and then using a combination of eqns. (1) and (2):

$$F_s = (F_c S_c(\nu_l) - F(\nu_l) S(\nu_l)) / (S_c(\nu_l) - S(\nu_l)) \quad (3)$$

F_c, $F(\nu_l)$ and $S(\nu_l)$ can all be measured, and $S_c(\nu_l)$ is estimated from the first term of eqn. (1), using values of K_c and r_c obtained by fitting eqn. (1) to the cell's contrast sensitivity curve.

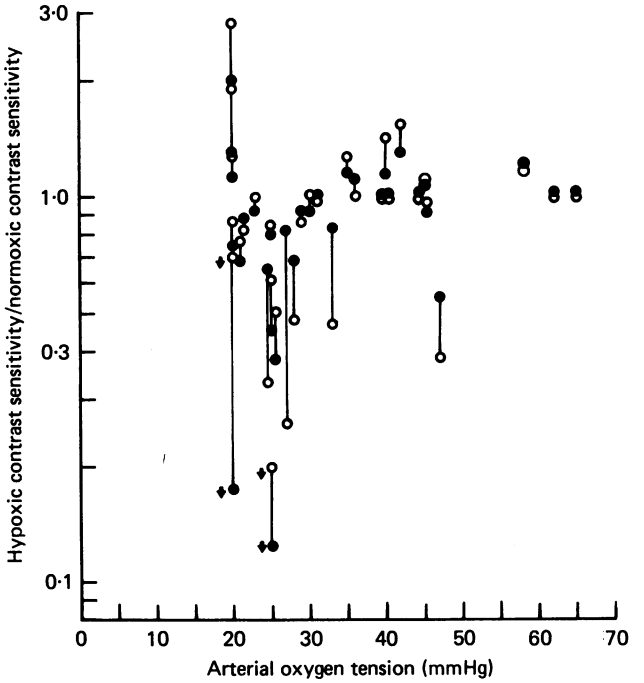

Fig. 7. Effect of hypoxia on the contrast sensitivity of the centre (F_c, filled circles) and the surround (F_s; open circles) of fifteen on- and three off-centre X cells. Descending arrows indicate cells for which the sensitivity was lower than could be measured.

The goal of the experiment then was to determine F_c and F_s. The procedure is illustrated for one cell in Fig. 6. First a contrast sensitivity curve was obtained. The continuous line in Fig. 6*A* is the fit of eqn. (1) to these data. The parameters, especially r_c and K_c, could be specified quite well, although the fit on this cell is a little better than average. Sensitivity was then tracked alternately at the high and low spatial frequencies denoted by the arrows in Fig. 6*A*. In these experiments more than one level of hypoxia was frequently studied before returning the animal to room air and the total time of a hypoxic episode was often more than 30 min. Fig. 6*B* illustrates the tracking and is analogous to the plots in Fig. 2. Four histograms were collected at one spatial frequency before changing to the other. The ratios of the hypoxic to normoxic sensitivities at the low and high spatial frequencies give the values $F(\nu_l)$ and F_c used in eqn. (3). In some cases (e.g. 5% O_2 in Fig. 6*B*) the duration of hypoxia was so short that no steady state was reached, so F_c and

$F(\nu_l)$ could not be estimated. For this cell the sensitivities of both the centre and surround dropped during hypoxia.

Fig. 7 shows the ratio of the sensitivity during hypoxia to that before hypoxia for the centre (F_c) and surround (F_s) as a function of arterial oxygen tension. Points for the centre and surround of each cell are connected. For most of these cells changes in the centre and surround were similar but usually not identical. The surround behaved much like the centre, in that its sensitivity did not usually change at arterial oxygen tensions above about 35 mmHg.

TABLE 1. Ratio of hypoxic to normoxic sensitivity at two high spatial frequencies for five X cells

Cell	Spatial frequency (c/deg)	Normoxic sensitivity	Hypoxic/normoxic sensitivity mean and (range*)
66/6	1·50	37	0·70 (0·58–0·82)
	2·0	13	0·76 (0·64–0·87)
66/13	1·50	22	0·56 (0·49–0·62)
	2·25	11	0·50 (0·40–0·61)
70/12	0·75	54	0·76 (0·61–0·77)
	1·62	8	0·67 (0·64–0·87)
67/5	0·62	44	0·70 (0·59–0·84)
	0·81	14	0·88 (0·57–1·19)
67/15	1·62	40	0·55 (0·21–0·78)
	2·0	12	0·76 (0·52–1·0)

* Range of ratio computed from 90% confidence intervals on sensitivity during normoxia and hypoxia.

In view of the fact that F_c could be greater or less than unity at a given oxygen tension, it is interesting that the changes in centre and surround were always in the same direction for a given pair of points. For the two cells represented by the lowest points in Fig. 7 relatively little can be said about the change in surround sensitivity, because in these two cases the sensitivity at both spatial frequencies dropped so low that it could not be measured. Under these conditions one gets only upper limits on $F(\nu_l)$ and F_c. F_s was calculated assuming that at both ν_l and ν_h sensitivity dropped to 1·25, but this is very crude, and perhaps the points for F_s should be closer to the ones for F_c.

Tracking at two high spatial frequencies. The assumption was made in the preceding section that K_c changed during hypoxia but r_c did not. This is important, because if r_c changed the change in centre sensitivity could not be characterized by the single parameter F_c, and the analysis of changes in the surround would be more difficult.

Theoretically, by measuring sensitivity changes at two high spatial frequencies, where the second term of eqn. (1) drops out, one can tell whether r_c or K_c changes. If only K_c changes, the ratio of hypoxic to normoxic sensitivities should be the same at all high spatial frequencies. A change in r_c or in both r_c and K_c would lead to different sensitivity ratios for different spatial frequencies.

For five cells the sensitivity was measured at two high spatial frequencies and the predominant change appeared to be in K_c. Table 1 gives the ratio of sensitivity

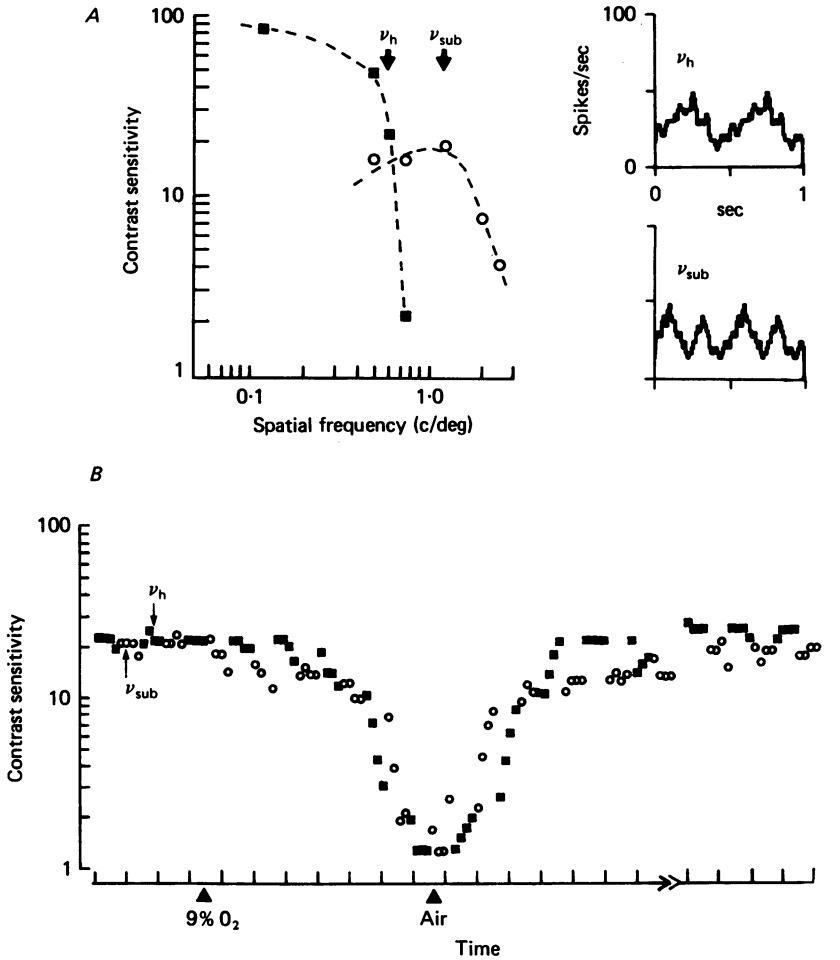

Fig. 8. *A*, contrast sensitivity of an on-centre Y cell to drifting gratings (filled squares) and to gratings with sinusoidal contrast reversal (open circles). On the right are histograms collected in response to a grating drifting at 2 c/sec at ν_h and to a grating whose contrast reversed at 2 c/sec at ν_{sub}. Histogram details are the same as in Fig. 6. *B*, contrast sensitivity as a function of time during hypoxia. Gas changes are indicated on the abscissa, where each division is 2 min. Breathing 9 % O_2 resulted in a P_{a,O_2} of 24 mmHg. The break in the record after hypoxia denotes 12 min when the sensitivity was gradually recovering.

during hypoxia to that before hypoxia at these spatial frequencies. Also given is the range of this ratio allowed by the 90 % confidence intervals on the sensitivity, derived from least squares fits of the contrast–response data obtained from the sensitivity tracking experiments. For the first three cells in Table 1 the ratio at the two spatial frequencies is the same, and for the other two it can at least not be stated that the ratio is different, because the range overlaps. Thus, while a small change in the size of the centre (r_c) cannot be ruled out entirely, the similarity of these ratios indicates that it is predominantly the peak sensitivity (K_c) which changes in hypoxia.

Y cells. The experiment on Y cells was a bit more straightforward. The surround

was not studied in Y cells because the low frequency fall in sensitivity was not pronounced over the range of available spatial frequencies. Instead, the effect of hypoxia on the non-linear subunits (Hochstein & Shapley, 1976*a*, *b*) was investigated.

Sensitivity was tracked alternately with a drifting grating of high spatial frequency and a stationary grating (of slightly higher spatial frequency) whose contrast

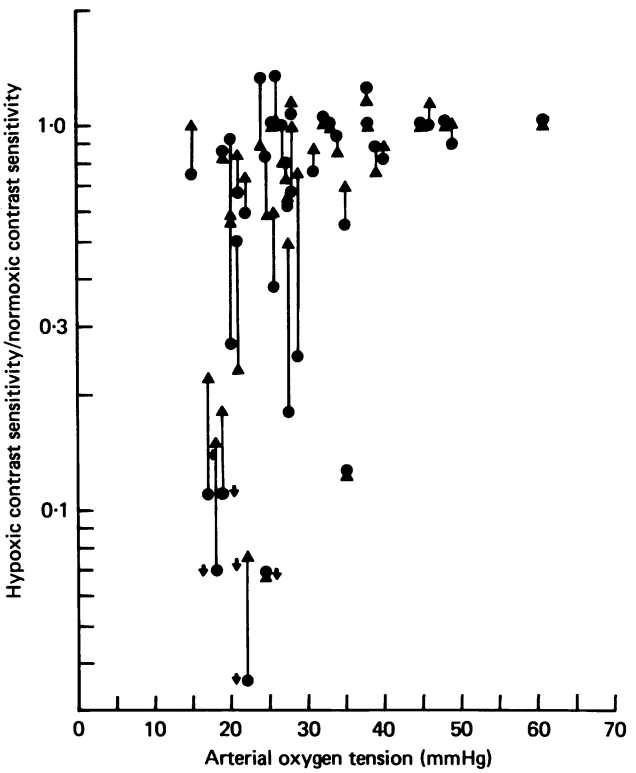

Fig. 9. Effect of hypoxia on the contrast sensitivity of the centre (circles) and the subunits (triangles) of eighteen on-centre Y cells. Descending arrows indicate cells for which the sensitivity was lower than could be measured.

reversed sinusoidally. The choices of spatial frequency are illustrated in Fig. 8*A*. It was possible to assess directly changes in the sensitivity of the centre by using the drifting grating and changes in the subunits by using the contrast reversal grating.

Fig. 8*B* shows an example of sensitivity tracking for a Y cell. In this case the sensitivity to both the drifting grating and contrast reversal grating fell at about the same rate to a level lower than could be measured, indicating a severe effect of hypoxia on both centre and subunits.

The ratio of hypoxic to normoxic sensitivities was estimated from plots like that in Fig. 8*B*, and Fig. 9 is a summary of this data.

Changes in the sensitivity of the centre and subunits were usually similar within a cell and, with one exception, they were always in the same direction. Where there was a difference between centre and subunits, the change in the sensitivity of the centre was larger in about 75% of the cases.

Oxygen measurements

The measurements of intraocular oxygen tension described below are called measurements of retinal oxygen tension. However, the electrodes actually recorded the oxygen tension of the vitreous humor near the retina, and the justification for referring to these as measurements of retinal oxygen tension is based on the oxygen distribution in the eye. The vitreous humor itself is avascular, and all its oxygen must diffuse from the retinal or choroidal circulations. However, the vitreous humor uses virtually no oxygen (Briggs & Rodenhauser, 1973), so that there is a very shallow

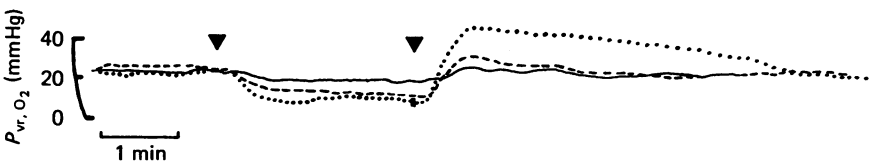

Fig. 10. Retinal oxygen tension during three successive episodes of hypoxia with 10% (dashed line), 15% (continuous line), and 5% (dotted line) oxygen. The break in the dotted line indicates that this run was 1·25 minutes longer than the other two, but otherwise these runs have not been scaled in any way. Calibration is approximate. (Cat 12.)

gradient of oxygen tension through the vitreous humor from the retina to the lens, about 2–3 mmHg/mm (Briggs & Rodenhauser, 1973; Linsenmeier, Goldstick, Blum & Enroth-Cugell, 1980). Because the gradient is shallow, oxygen measurements made in the vitreous humor less than 500 μm away from the retinal surface will be within 1 mm of the average oxygen tension of the inner layers of the retina at steady state.

Examples of the transient response of retinal oxygen tension to step changes in inspired oxygen concentration are shown in Fig. 10. The measured time course depends on the distance from the electrode to the retina (Linsenmeier *et al.*, 1980), but when the electrode is within about 200 μm of the retinal surface the time course is relatively undistorted by the vitreous humor. A new steady state was achieved within 2 min of a decrease in inspired oxygen concentration. The transient response was non-linear in that the fall in retinal oxygen tension at the beginning of hypoxia was slower than the recovery at the end of hypoxia. Furthermore, there was an overshoot following the return to air breathing, and as shown in Fig. 10, this was larger after more severe degrees of hypoxia. A return of retinal oxygen tension to the base line sometimes took as long as 12 min. The time course of changes in oxygen tension was, therefore, similar to the time course of sensitivity changes, but sensitivity did not overshoot following hypoxia. The overshoot in retinal oxygen tension is thought to be an indication of retinal oxygen autoregulation. During hypoxia the retinal vessels dilate (e.g. Hickam & Frayser, 1966) and at the end of hypoxia a large amount of oxygen flows through the still dilated vessels, causing the overshoot. Similar transients have been reported for the optic disk by Ernest (1973) and for the brain by Metzger (1973).

Steady-state values of retinal *vs.* arterial oxygen tension from ten cats breathing 21, 15, 10, 7·5 and 5% oxygen are shown in Fig. 11. Simultaneous measurements of

arterial and retinal oxygen tension were made before hypoxia, and after retinal oxygen tension had stabilized during hypoxia. Measurements of retinal oxygen tension were made when the end-tidal CO_2 was in the range of 4·5–5 %. Two straight lines were fitted to the data, though a sigmoid curve would probably have fitted equally well. The lines are:

$$P_{vr,O_2} = 0{\cdot}14\ (P_{a,O_2}) + 4{\cdot}95 \quad \text{for } P_{a,O_2} > 35 \text{ mmHg}$$
$$P_{vr,O_2} = 0{\cdot}62\ (P_{a,O_2}) - 11{\cdot}80 \quad \text{for } P_{a,O_2} < 35 \text{ mmHg}$$

Here P_{a,O_2} is arterial oxygen tension and P_{vr,O_2} is the oxygen tension in the vitreous humor near the retina (retinal oxygen tension). Arterial and retinal oxygen tension were measured in two other cats (24 and 40), but the comparison of electrode current with the calibration indicated that the retinal oxygen tension was negative during severe hypoxia. Values obtained from these animals are given in the legend of Fig. 11. No allowance has been made for possible errors in the other direction, when an inaccurate calibration might have given values of retinal oxygen tension which were too high.

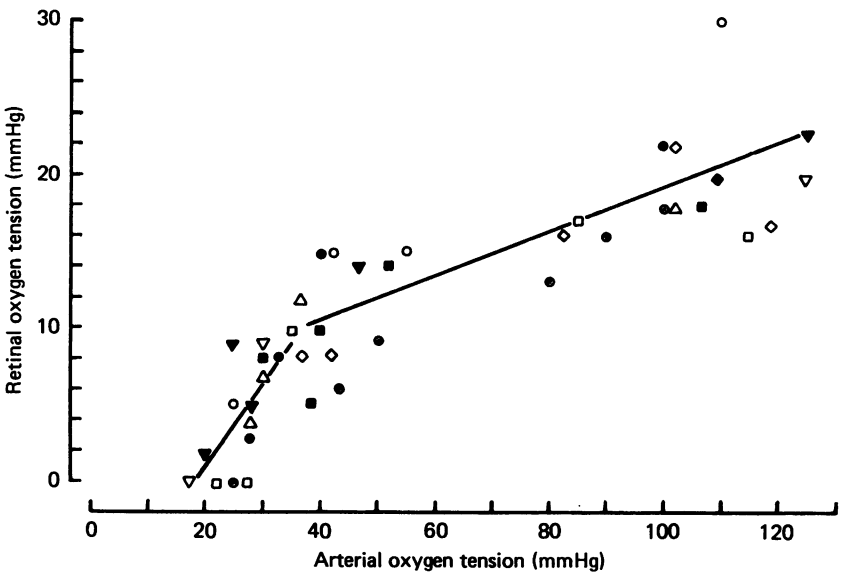

Fig. 11. Steady-state values of retinal oxygen tension *vs.* arterial oxygen tension. Ten cats are each represented by a separate symbol. Lines are least-squares fits for $P_{a,O_2} < 35$ mmHg and for $P_{a,O_2} > 35$ mmHg as described in text. Data from two cats in which some measured values of retinal oxygen tension were negative (retinal oxygen tensions of −7, −7, 0, 20 and 6 mmHg for arterial values of 29, 31, 33, 75 and 100 mmHg) have been excluded.

Clearly the retinal oxygen tension is well regulated over a wide range of arterial oxygen tensions, corresponding reasonably well with the range over which ganglion cell sensitivity is normal (see Figs. 4, 7 and 9). Data similar to those shown in Fig. 11 have been obtained by Alm & Bill (1972) who did not study arterial oxygen tensions below 45 mmHg. The average slope of their plots of retinal *vs.* arterial oxygen tension for five cats is about 0·18 mmHg/mmHg, in good agreement with the slope found here.

DISCUSSION

These results demonstrate that ganglion cell sensitivity and mean firing rate (in the presence of continuous stimulation) are maintained at normal levels over a wide range of arterial oxygen tensions, apparently because retinal oxygen tension is well regulated. Over the range in which retinal oxygen tension falls moderately, ganglion cell contrast sensitivity is normal. When retinal oxygen tension changes more than about 10 mmHg the sensitivity usually drops. The regulation of oxygen tension certainly depends on vascular adjustments within the retina (e.g. Hickam & Frayser, 1966) but blood pressure is also important. Decreases in retinal oxygen tension and sensitivity were observed most often when the compensatory blood pressure increase at the beginning of hypoxia could not be sustained.

The fact that oxygen and ganglion cell measurements were made in some cases on different animals was not considered to be a serious problem. First, the conditions were almost identical in both types of experiments and secondly the oxygen electrode was capable of recording only the average oxygen tension, not that at any particular ganglion cell.

Comparison with physiology and psychophysics. These results extend work which has been done on retinal massed potentials. Bos (1968) found that the e.r.g. of the cat changed only when the haemoglobin saturation was less than about 50%, corresponding to an arterial oxygen tension of about 37 mmHg in normal cats (Herbert & Mitchell, 1971). The e.r.g. was slightly less resistant to hypoxia in animals studied by Adams, Perez & Dawson (1973). They found that an inspired oxygen concentration of 12% (which would have produced an arterial oxygen tension of about 40 mmHg in this study) caused a reduction in the amplitude of the b wave to 20–70% of control. At this level of hypoxia, Adams *et al.* (1973) found that a light-evoked potential recorded from the optic nerve was unchanged, but slightly more severe hypoxia (8 or 10% O_2) caused the optic nerve response to drop to 0–60% of control. Their work is in agreement with that of Massopust *et al.* (1966) who found that the response of the optic chiasm was reduced to about 40% of control in animals breathing 9·1% O_2. Despite the differences in techniques, these results on the optic nerve massed potential agree quite well with results of the present study in showing a sudden breakdown of retinal function at an arterial oxygen tension between 30 and 40 mmHg.

Whether other parts of the nervous system resist hypoxia as well as the retina is not clear, because comparable data are limited. On the one hand, Kogure, Scheinberg, Utsunomiya, Kishikawa & Busto (1977) found that the rat e.e.g. changed only at arterial oxygen tensions below 25 mmHg, and Branston, Symon, Crockard & Pasztor (1974) found that cerebral blood flow could be reduced to about a third of normal before the amplitude of evoked potentials in the baboon cortex decreased. On the other hand, the activity of chemoreceptors (Acker, Keller, Lübbers, Bingmann, Schulze & Caspers, 1973) and spinal cord interneurones (Speckmann, Caspers & Sokolov, 1970) begins to change at relatively high oxygen tensions. However, these types of cells fire faster during mild hypoxia, and thus are quite different from cortical (Silver, 1973) or retinal cells, in which the firing rate typically drops.

It is generally accepted, on the basis of psychophysical evidence, that the visual

system is quite sensitive to changes in inspired oxygen tension, and in this context the resistance of ganglion cells to hypoxia may appear puzzling. There may be real discrepancies between psychophysical data and the electrophysiological work presented here, due to species differences, or to the fact that experimental animals are anaesthetized and paralyzed. However, it is worth noting that the psychophysical effects of hypoxia (1) must involve effects on cortical as well as retinal processing and (2) are rather small. For example, Ernest & Krill (1971) measured thresholds after dark adaptation with a 5 deg test spot at an eccentricity of 5 deg, and found elevations of 0·42 log units in cone threshold and only 0·15 log units in rod threshold, in subjects breathing 10 % oxygen. Changes in the sensitivity of light adapted human subjects are even smaller at this degree of hypoxia (McFarland *et al.*, 1944).

Centre, surround and subunits. While there were frequently differences in the effects of hypoxia on the centre and surround of individual X cells, the effects were not consistent, and there were hardly any cells for which the sensitivity of the surround changed but that of the centre did not, or vice versa. The centre and subunits of Y cells were also about equally susceptible to hypoxia. It might have been more interesting if the surround or subunits had failed at an arterial oxygen tension substantially above that at which the sensitivity of the centre changed. But it now appears that lateral pathways through the retina (i.e. surround) and pathways which might be expected to use more synapses than the centre (i.e. surround and subunits), are not necessarily more susceptible to hypoxia. In fact if there is a difference between the centre and subunits of Y cells, the centre is slightly more susceptible to hypoxia.

Some aspects of retinal electrophysiology do fail more rapidly during anoxia than others. Granit (1933) was the first to show that the b wave of the electroretinogram failed before the a wave. Noell (1951), among others, confirmed this result, and showed that the b wave also failed before impulse conduction in the optic nerve. More recently, Drujan *et al.* (1971) found that signals could be carried through horizontal cells located in an anoxic area of carp retina after transmission of signals from receptors to horizontal cells in that region was abolished. These results are all consistent with the idea that anoxia disrupts some early stage of retinal processing, rather than affecting all types of cells equally. The present work shows that this apparently selective effect of hypoxia on some cells is not reflected in differential effects on the various components of the ganglion cell receptive field. This suggests that the cell type or synapse which is affected is shared by the pathways used by the centre and surround of X cells and the centre and subunits of Y cells, so that the effects on these mechanisms can be similar. This cell or synapse must then be either early in the retina, before different pathways have become distinct, or else late in the retina, after signals from the pathways have converged. Based on earlier work (e.g. Noell, 1951) and on the distribution of the retinal vasculature, one would think that an effect early in the retina is more probable. It should be pointed out, though, that the present data taken alone do not exclude the possibility that hypoxia acts rather diffusely on all types of cells.

Limitations. Some of the limitations of the present work should be stated explicitly. First, only X and Y cells were studied, and, while the susceptibility of these cell types to hypoxia appeared to be similar, other types of ganglion cells (Stone &

Fukuda's (1974) W cells; Cleland & Levick's (1974*a* and *b*) sluggish and non-concentric cells) could react differently.

Secondly, the influence of blood glucose on the behaviour of cells during hypoxia has not been considered. Other experiments have suggested that the visual system can be partially protected from hypoxia if glucose levels are high (McFarland, Halperin & Niven, 1945; Ames & Gurian, 1963). Blood glucose was not measured in the animals used for these experiments, but in animals prepared similary plasma glucose levels were on the order of 150–200 mg %. This hyperglycemia, which was probably a result of the urethane anaesthesia (Reinert, 1964), may partially account for the resistance of ganglion cells to hypoxia.

Finally, the index of retinal oxygen tension used here is appropriate only for the inner retinal layers. It is difficult to measure or estimate the oxygen tension of the outer retinal layers, which are avascular and are supplied by diffusion from the retinal and choroidal circulations. Calculations by Dollery, Bulpitt & Kohner (1969) and by Linsenmeier (1978) of the profile of oxygen tension through the retina suggest that in the avascular region the oxygen tension will be lower than in the inner retina. At an arterial oxygen tension of 50 mmHg even a conservative analysis indicates that the oxygen tension somewhere in this region will be zero. If this is true, it is somewhat surprising that ganglion cell sensitivity does not decrease at higher arterial oxygen tensions. Possibly the avascular region of the retina is affected minimally during hypoxia because glycolysis supplies a large part of the energy (Lowry, Roberts & Lewis, 1956).

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