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The Effect of *In Vivo* Retinal Cooling on the Electroretinogram of the Rabbit

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Purpose. **Studies reporting the effect of retinal cooling on the electroretinogram of mammals have, in most cases, made use of an *in vitro* approach where the temperature of the retina was lowered by reducing the temperature of the bathing media. The purpose of our study was to investigate, in rabbits, the effect of *in vivo* retinal cooling using an experimental approach never before reported in order to determine if some of the temperature-related ERG effects previously shown could have been, in part, amplified by alterations in the physiological status of the retina due to preparation for *in vitro* study.** ***Methods.*** **In order to reduce the temperature of the retina, a 20 gauge plastic tubing was coiled around the eye from the limbus to the optic nerve head and glued to the sclera. Cold (15°C) tap water entered the tubing at the limbal extremity and exited (18°C) at the optic nerve extremity. Intraretinal temperature was measured to be within 1°C of that of the circulating water.** ***Results.*** **Our results indicate that with progressive retinal cooling the a- and b-waves are gradually reduced to 66.9 ± 17.3 and 90.9 ± 10.4% of control respectively. The most dramatic temperature induced ERG modifications were observed in the oscillatory potential recordings where the mean summed OP amplitude ($OP_2 + OP_3 + OP_4$) was reduced to less than 23.9 ± 13.5% of control with OP_2 being the least affected. The peak times of all the ERG components were significantly delayed with cooling.** ***Conclusions.*** **Of all the ERG components examined, the OPs were those most severely affected by our manipulation. We believe that our results constitute further evidence in support of the concept that the OPs are more sensitive to retinal disturbance than the b-wave.**

Electroretinogram Retina Temperature b-Wave Oscillatory potentials Rabbit *In vivo*

INTRODUCTION

The effect of retinal cooling on the electroretinogram has been investigated in numerous species (Adolph, 1985; Armington & Adolph, 1984; Dawson, Hope & Bernstein, 1971; Niemeyer, 1975; Schellart, Spekreijse & van der Berg, 1974; Thorpe, 1973; Winkler, 1972) including man (Horiguchi & Miyake, 1991; Zilis, Chandler & Machemer, 1990). *In vivo* experiments were mostly conducted in fishes (goldfishes and carps) where the temperature of the retina was lowered either through whole body immersion in refrigerated aquariums (Dawson *et al.*, 1971; Schellart *et al.*, 1974) or by pumping cold water through the gills (Thorpe, 1973; Schellart *et al.*, 1974). *In vitro* retinal cooling was usually obtained by lowering the temperature of the bathing media (Adolph, 1985; Armington & Adolph, 1984; Winkler, 1972) or that of the circulating perfusate in the case of isolated intact cat eyes (Niemeyer, 1975). With few exceptions (Thorpe, 1973; Schellart *et al.*, 1974) a progressive reduction in the temperature of the retina progressively reduced the amplitude and increased the timing of all ERG components (Dawson *et al.*, 1971) with the a-wave being the least affected (Adolph, 1985; Armington & Adolph, 1984). Maximal effect was usually characterized by a complete extinction of all the ERG components which was reached, in homeotherms, at retinal temperature varying between 15°C (Winkler, 1972) and 26°C (Niemeyer, 1975). The reasons for the latter temperature variability cannot be explained other than as a consequence of the different experimental approaches used.

Although the above results would suggest that retinal physiology is highly temperature dependent one cannot rule out the possibility that other contributing factors, inherent in the experimental approach used, might have amplified the ERG temperature dependence. For instance a possible systemic contribution in whole body cooling or an absence of necessary retinal nutrients in the eye cup preparation. To investigate this issue we developed a unique method allowing for the cooling of the retinal tissue *in vivo* with the eyeball intact. Results obtained suggest that the OPs are more sensitive than the a- and b-wave to the retinal stress thus created.

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METHODS

The experiments were conducted on 10 New-Zealand rabbits (2–3 kg) which were anesthetized with an intravenous injection of urethan (1 g/kg; 25% solution). A tracheostomy was performed and the animals were placed in a stereotaxic frame (David Kopf), paralyzed with gallamine thriethiodide (15 mg/kg) and artificially ventilated (30 strokes/min, 30 cm^3/stroke, duration of inspiration: 40%). The extraocular tissues, including the upper and lower eye-lids were surgically removed. A 20 gauge plastic tubing (30 cm in length) obtained from a Butterfly 23 infusion set (Venisystem™, Abbott Laboratories Ltd) was coiled around the eye from the limbus to the optic nerve head and glued to the sclera with Krazy glue™ (Fig. 1). The limbal extremity was then connected to another tubing of approx. 10 m in length, most of which was buried in a plastic container filled with crushed ice and water, and whose free extremity was connected to the water tap. By controlling the flow of water circulating in the above circuit, the temperature of the water was reduced to approx. 15°C (measured with a YSI Telethermometer inserted between the refrigerating tubing and the sclera). The water exited the circuit (at the optic nerve head) with a temperature of approx. 18°C (measured as above). The latter temperature range was chosen to compare with previously published data obtained from homeotherms (Winkler, 1972; Niemeyer, 1975). In one separate experiment the intraretinal temperature was measured with a YSI model 513 20 gauge needle temperature probe inserted, through a canula, at the limbus. Intraretinal (at b-wave reversal depth) temperature measurements stabilized to within 1°C of that measured on the sclera after less than 10 min of cooling, confirming that our device was efficient in cooling the retina. The effect of retinal cooling was considered maximal, for the previously mentioned temperature, when no significant amplitude and peak time differences could be noted between consecutive recordings. The latter usually occurred within the first 10 min of retinal cooling. Similarly, given that all the averages were performed on-line we considered that recovery was complete once the timing of the ERG parameters (mostly the a- and b-waves) returned to their control values as judged from oscilloscope monitoring. The latter methodological approach was chosen in part due to the high reproducibility of peak time measurements and also because the effect of temperature was more pronounced on the peak time than on the amplitude of the b-wave (i.e. the ERG wave most easily monitored with an oscilloscope).

The electroretinograms were recorded using a Grass platinum subdermal electrode (type E2) inserted (at the limbus) in the anterior chamber of the eye, after having anesthetized the cornea with 0.5% proparacaine hydrochloride. During insertion great care was taken to avoid

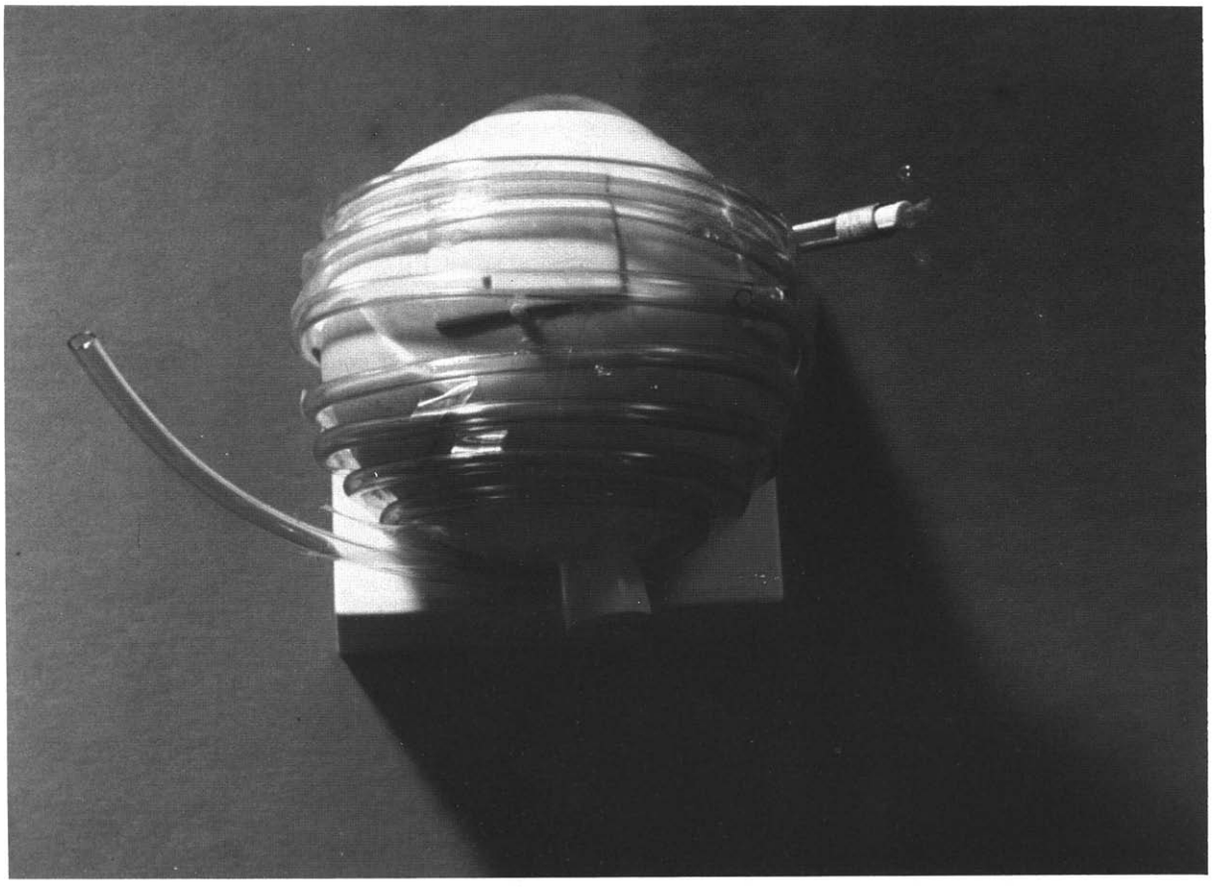

FIGURE 1. Representation of the montage used to produce the retinal cooling. Cold tap water entered the coiled tubing at the limbus extremity and exited at the optic nerve level (see text).

contact with either the iris or the corneal endothelium with the tip of the needle electrode since it could lead to a gradual opacification of the ocular media and thus prevent the continuation of the experiment. The pupil was dilated with 0.5% cyclopentolate hydrochloride and ground and reference electrodes (Grass type E2) were inserted in the scalp. The biopotentials were recorded using two Grass P-511 analog preamplifiers. The conventional ERGs were amplified 2000 times with a bandwidth of 1–1000 Hz (6 dB of attenuation) while the oscillatory potentials were amplified 10,000 times with a narrower bandwidth of 100–1000 Hz (6 dB of attenuation). ERGs were evoked by flashes (5 $cd \cdot m^{-2} \cdot sec$; Grass PS-22 photostimulator) of white light (20 μsec in duration; one flash every 1.024 sec) delivered against a photopic background of 25 $cd \cdot m^{-2}$ provided with a backlit tangent screen of 20 × 20 cm positioned at 15 cm from the rabbit eye (Benoit & Lachapelle, 1990). Averages of responses to 25 flashes were taken with a Nicolet Med-80 signal averager and stored on floppy diskettes for further analysis. Finally, it should be noted that our cooling procedure did not modify the intraocular pressure (IOP), as measured on two separate occasions by applanation tonometry with the rabbits lying on their side. Measurements performed prior to initiating the cooling procedure (but with the tubing and recording electrode in place) and at maximal effect (after more than 10 min of cooling) revealed that the IOP remained stable at approx. 10 mm Hg. This relatively low IOP could probably be explained by the high level of anesthesia as well as by the limbal puncture necessary to introduce the recording electrode.

Data analysis consisted in measuring the amplitudes and peak times of the a- and b-waves in the 1–1000 Hz tracings and of each major OP in the 100–1000 Hz recordings. Identification of the different components was performed according to a method previously described (Lachapelle & Blain, 1990). The amplitude of the a-wave was measured from baseline to a-wave trough while the amplitude of the b-wave was measured from the trough of the a-wave to the peak of the b-wave. In the 100–1000 Hz tracings, the amplitudes of the OPs were measured from trough to peak except for OP_2 which was measured from baseline to peak since the trough between OP_1 and OP_2 was often difficult to determine. The effect of retinal cooling was examined for individual OPs as well as collectively with the summed OP amplitude (SOPs) variable (e.g. $OP_2 + OP_3 + OP_4$). All latencies were measured from flash onset to the peak of the waveform. Statistical significance was determined with the use of a Student t-test. Animal experimentation was performed in accordance with the guidelines of the Association for Research in Vision and Ophthalmology (ARVO).

RESULTS

Figure 2 illustrates representative ERGs (A,C,E) and OPs (B,D,F) recorded from three different rabbits (A–B, C–D, E–F) before (tracings C), during (time in minutes at left of each tracing) a progressive lowering of retinal temperature and following recovery (tracings R). Group data are illustrated in Table 1. With retinal cooling the amplitude of all the retinal potentials examined are significantly attenuated with the OPs being the most affected and the b-wave the least. Retinal cooling also significantly increased the peak time of all the retinal potentials examined. The peak time of the a-wave increased by 3.8 ± 2.1 msec while that of b-wave increased by more than 11.3 ± 3.8 msec. Of all the OPs, the peak time of OP_2 was that least delayed by retinal cooling increasing by only 4.4 ± 1.8 msec compared to 8.5 ± 4.8 msec for OP_3 and 10.4 ± 3.3 msec for OP_4 respectively. Due to the differential effect of retinal cooling on the peak times of individual OPs, progressive retinal cooling also significantly increased the interpeak intervals by 4.0 ± 3.0 msec for the OP_2–OP_3 interval and by 3.4 ± 1.6 msec for the OP_3–OP_4 one. With rewarming all peak time measurements returned to normal control values. Similarly the amplitudes of the a-wave, b-wave,

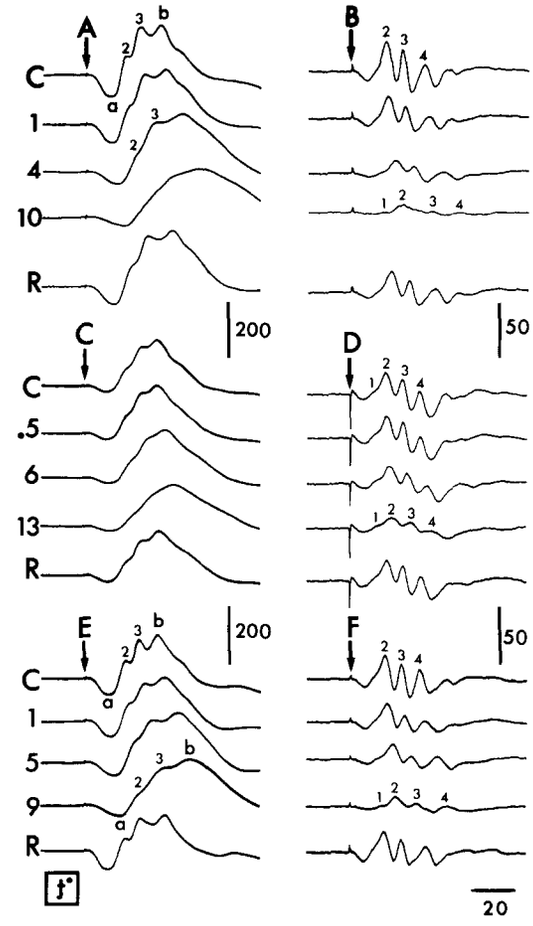

FIGURE 2. Representative ERG (A,C,E) and OPs (B,D,F) recorded (averages of 25 flashes) from three different rabbits (A–B, C–D, E–F) prior to (control tracings: C) and at regular time intervals (indicated in minutes at left of each tracings) following the onset of retinal cooling. Tracings R indicate recovery following warming of the circulating water. The ERG components are identified as: a (a-wave), b (b-wave), 2 (OP_2) and 3 (OP_3). The OPs on the OP selective recordings are identified numerically. Vertical arrows identify flash onset. Response is preceded by a 20 msec baseline recording. Calibration—horizontal, 20 msec; vertical, 200 μV (ERG) and 50 μV (OPs).

TABLE 1. Summary of amplitude and peak time measurements obtained from 10 rabbits

	Control	Cold	Recovery
Amplitude (% of control)			
a-wave	100	66.9 ± 17.3*	103.5 ± 19.2
b-wave	100	90.9 ± 10.4*	99.5 ± 5.6
OP_2	100	38.8 ± 15.4*	92.3 ± 11.5
OP_3	100	19.3 ± 17.3*	91.7 ± 11.5
OP_4	100	20.4 ± 10.8*	84.5 ± 14.7*
SOPs	100	23.9 ± 13.5*	89.2 ± 8.8*
Peak time (msec)			
a-wave	11.0 ± 1.1	14.8 ± 2.5*	11.5 ± 1.2
b-wave	33.4 ± 2.1	44.9 ± 5.1*	35.0 ± 2.1
OP_2	15.1 ± 0.3	19.7 ± 1.7*	15.6 ± 0.6
OP_3	22.8 ± 0.7	29.7 ± 3.7*	23.4 ± 1.0
OP_4	31.8 ± 1.8	41.9 ± 5.2*	33.1 ± 1.9
OP_2–OP_3	7.6 ± 0.4	10.1 ± 3.1*	7.8 ± 0.5
OP_3–OP_4	8.9 ± 1.6	12.2 ± 3.9*	9.6 ± 1.8

Due to intersubject variability, statistical significance for amplitude measurements were obtained by testing the cold and recovery means against the control 100% value (Student *t*-test, single sample; $\alpha = 0.01$) while peak time measurements were tested (Student 2-tailed paired *t*-test at $\alpha = 0.01$) between the control and cold (measured at maximal effect) data and between the control and recovery data. *Statistically different values.

OP_2 and OP_3 returned to values not significantly different from control while the amplitudes of OP_4 and SOPs, although demonstrating a significant recovery, were still significantly lower than control values.

In all the experiments reported above the tubing used to cool the retina was glued on the sclera from the limbus to the optic nerve. In order to determine if a lesser amount of tubing could also yield similar results we conducted an experiment where only two loops of tubing were glued to the sclera thus limiting retinal cooling to the first 4–5 mm posterior to the limbus. Results of this experiment are presented in Fig. 3. As illustrated, with retinal cooling there is a progressive reduction in the amplitude of OP_4 which reaches, some 20 min after the onset of cooling, an amplitude which is approx. 25% of control. In contrast neither the amplitude of OP_2 nor that of OP_3 appear to be significantly altered by this procedure; their amplitudes oscillating at a value around 90% of control. Similarly a close inspection of the tracings also reveals that the peak time of OP_4 is delayed with retinal cooling while that of OP_2 and OP_3 are not measurably affected. Clearly OP_4 is the only OP significantly modified when retinal cooling is restricted to the peripheral retina.

DISCUSSION

To our knowledge our study is the first one to report, in mammals, the effect of a progressive retinal cooling on the ERG using an *in vivo*, intact eye approach. Based on amplitude criteria, our results clearly demonstrate that of all the retinal potentials those most severely affected by the cooling of the retina are the OPs with OP_2 being the least affected at 38.8 ± 15.4% of control amplitude while OP_3 and OP_4 are similarly reduced to 19.3 ± 17.3 and 20.4 ± 10.8% of control amplitude respectively (Table 1). In comparison the a- and b-waves were attenuated to 66.9 ± 17.3 and 90.9 ± 10.4% of control respectively. The above results thus clearly point out the fragile nature of the OPs, a finding which reinforces the concept that in clinical electroretinography, a careful analysis of OP responses in humans could reveal, long before a- and b-wave involvement, an underlying pathological process even at the subclinical stage (Lachapelle & Little, 1992). However, the progressive delay and eventually the removal of the OPs from the ERG

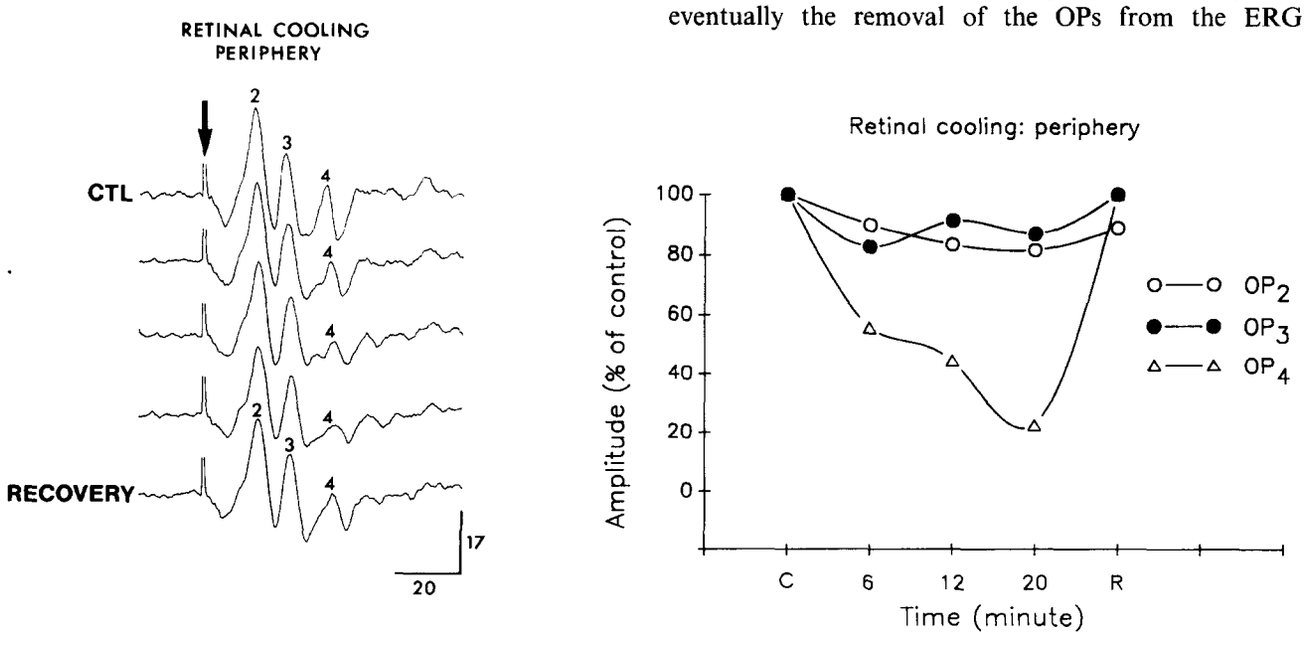

FIGURE 3. Representative example of OP recordings obtained prior to (CTL), during (at 6, 12 and 20 min) and following (recovery) the onset of retinal cooling restricted to the peripheral retina. Data is graphically reported at right of the figure. Note that OP_4 is the only OP modified by this procedure. Vertical arrow indicates flash onset. Calibration—horizontal, 20 msec; vertical, 17 μV.

responses, and in particular of OP_4, appears to have a significant impact on the peak time of the resulting b-wave. At maximal effect the peak time of the b-wave is delayed by more than 11.3 ± 3.8 msec a value not significantly ($P > 0.05$) different from the 10.4 ± 3.3 measured for OP_4. The contribution of OP_4 to the peak time of the photopic b-wave was previously reported elsewhere (Lachapelle, 1987; Peachey, Alexander, Derlacki, Bobak & Fishman, 1991).

As seen in Table 1, although all peak time values returned to control upon rewarming, not all amplitudes did. We do not believe that the latter should be interpreted as evidence that our procedure resulted in permanent injuries to the retinal tissue. As noted in the Method section, the peak time more than the amplitude was chosen as an on-line criterion for recovery. Thus the results presented in Table 1 could simply indicate that the peak time parameters recovered faster than amplitude ones. Notwithstanding the above, our procedure did generate results showing a complete recovery. Such an example is illustrated in Fig. 2 (C,D) were the peak times and amplitudes of all the ERG waves (a-, b-waves and OPs) measured in tracings R are identical to those measured in the control tracings.

As shown in Fig. 3, only OP_4 is significantly modified in amplitude and timing when the cooling probe is limited to the peripheral retina. It could be that of all the OPs, OP_4 is that most sensitive to modification in retinal temperature. Results presented in Table 1 could support this interpretation given that, of all the OPs, OP_4 showed the largest peak time increment following retinal cooling and also recovered the least compared to the other OPs (Table 1). However, in previous studies (Lachapelle, 1994; Lachapelle, Little & Benoit, 1990) we presented clinical evidence suggesting that each of the suprathreshold photopic OPs appeared to have a concentric organization where OP_2 would be generated from the central retina (e.g. close to the macula) and OP_4 would be generated in more peripheral retinal areas. The results illustrated in Fig. 3 could also bring support to this claim. Clearly more research, such as limiting the cooling procedure to other regions of the retina, is needed to clarify this point.

Previous attempts to study the effect of retinal cooling *in vivo* were performed on goldfishes and carps either raised in refrigerated aquariums or cooled with cold water pumped through their gills. The effect of retinal hypothermia on ERG generation was also investigated in human subjects undergoing vitreous surgery (Horiguchi & Miyake, 1991; Zilis *et al.*, 1990). The other species investigated, including cats and rats, were all performed using an *in vitro* approach (eye cup preparations or perfused intact eyes). The results obtained with the *in vivo* approach are contradictory; a finding which might be explained by the differences in methodological approaches used to reduce the retinal temperature as well as the extent of hypothermia obtained. For instance Thorpe (1973) compared goldfishes raised at 25°C with goldfishes raised at 15°C and found no significant effect on the a-wave and minimal effect on the b-wave while Schellart *et al.* (1974) using a similar experimental approach reported no significant changes in ERG components. In contrast using a similar approach but with colder temperatures, Dawson *et al.* (1971) showed that all ERG components, including the OPs, disappeared within 15 days of exposure at a temperature of 6°C. These ERG changes were found to be correlated with a depletion of the cone outer segments. It is important to note that in few of the *in vivo* experiments reported above was the retinal temperature actually measured. It was assumed that the internal temperature of these poikilotherms would gradually equalize with that of their environment a physiological response which should have a direct consequence on the temperature of the circulating fluids and consequently on that of the surrounding tissues including the retina. Hiroguchi and Miyake (1991) also demonstrated a temperature effect in ERGs recorded from patients undergoing vitreous surgery. They showed that when the temperature of the irrigating solution was lowered from 35 to 27°C there was a rapid reduction in the amplitude of the b-wave which was accompanied by a significant increase in peak time. However, the technique used to elicit the ERG (flickering light) prevented them from commenting on the OPs. Studies reporting the effect of *in vitro* retinal cooling in homeotherms all showed a progressive attenuation in the amplitude with an increase in timing of all the ERG components including the OPs as the retinal temperature is lowered. There was a complete extinction of all ERG components at temperature ranging between 26 C (Niemeyer, 1975) and 15°C (Winkler, 1971), that is a temperature range similar to that used in our study. Our results would therefore suggest that, *in vivo*, the retinal tissue is more resistant to cold temperature than what was suggested from the *in vitro* studies or that the effects of hypothermia on the retina are amplified when an *in vitro* model is used.

Why is it that our method of producing retinal hypothermia was so detrimental to the retinal OPs, a feature not previously reported by others? It could be that our cooling device triggered a vasoconstrictive reaction of the retinal blood vessels and consequently induced a pseudo-ischemic reaction. The ERG oscillatory potentials were previously shown to be highly sensitive to retinal ischemia, such as that seen in diabetic retinopathy (Speros & Price, 1981), a finding that would be supportive of our interpretation. For some, our findings might be partly explained by a decrease in ocular blood flow due to the occlusion of the vortex veins resulting from the undue pressure exerted by the plastic tubing surrounding the eye. While it is difficult to rule out that the latter could have contributed, on two separate occasions we did not notice an increase in IOP that the presumed reduction in ocular blood flow should have produced. It could be that the puncture performed at the limbus, to insert the ERG recording needle, acted as a supplementary exit for the excess aqueous humor. However, it is important to remember that our cooling device remained in place throughout the experimentation and consequently the possibility that the reported

effect could have resulted from a reduction in ocular blood flow as previously described is, we believe, ruled out by the fact that, with rewarming, we were able to restore to their original values most of the ERG components despite the fact that the alleged undue pressure on the vortex veins was still present. Notwithstanding the above it is difficult to completely rule out a contributory effect of the vascular system to our results since its presence is one of the major differences which distinguishes our approach from the *in vitro* one and could explain why it took as much as 10 min to reach maximal effect. The timing of the OPs (peak times and interpeak intervals) were also significantly increased with retinal cooling suggesting a reduction in the frequency domain of the OPs. In that respect it is noteworthy to remember that OPs are usually extracted from the ERG response using a bandwidth restriction procedure. It is obvious that amplitude measurements and comparisons will be meaningful provided that the frequency domain of the OPs does not drop significantly, and surely not below the low frequency cut-off of the recording bandwidth which was, in this study, fixed at the recommended 100 Hz. The latter explanation was offered, in a previous study, to explain the lack of recordable OPs in retinal potentials obtained from the immature rabbit (Gorfinkel, Lachapelle & Molotchnikoff, 1988). One wonders if this could not partly explain our results. Another explanation is offered from studies reporting the effect of reversible cooling on single cell recording at the cortical level. Results from these studies indicate that cooling at 20°C will abolish all synaptic activities while cooling at 10°C will abolish all cellular activities (Brooks, 1983). Given our estimate of the intraretinal temperature at maximal cooling (15–18°C) our results could also suggest that the OPs signal intraretinal synaptic activities a concept often raised by others (Karwoski & Kawasaki, 1991). Our technique offers not only the possibility to further investigate these issues but also, given the *in vivo* intact eye approach used, investigate the effect of retinal cooling on the post-retinal processing of the retinofugal signal.

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