The Human Electro-oculogram: Interaction of Light and Alcohol

Geoffrey B. Arden and Janet E. Wolf

Purpose. To investigate the production of the voltage changes evoked in the retinal pigment epithelium (RPE) by light and alcohol and the interaction of these agents.

Methods. The eye movement potential in humans was intermittently recorded to standard horizontal excursions for long periods during which either retinal illumination was altered or ethyl alcohol was administered by the oral, intragastric, or intravenous route. In other experiments, both light and alcohol were administered.

Results. Alcohol and light produced near identical corneofundal voltage changes (positive and then negative) over more than 40 minutes. Differences in timing between alcohol and light increases are explicable by the delays in alcohol absorption. Weak background light suppressed the effect of light steps, and low levels of background alcohol suppressed the response to subsequent doses. Backgrounds of one agent did not affect the voltage changes caused by the other. Minimal alcohol effects were seen after administration of 1 g orally or 270 mg intravenously—that is, doses that produced undetectable changes in breath alcohol. The semisaturating oral dose was approximately 20 mg/kg.

Conclusions. Alcohol and light act through separate pathways to form a final common pathway inside the RPE cell that is responsible for triggering the timing of the slow oscillatory changes of EOG voltage. The sensitivity and duration with which alcohol affects the RPE are comparable with the effect of melatonin or dopamine, although only the former interacts with light similarly to alcohol. Transient modulation of the acetylcholine (Ach) neuronal receptor occurs at similar sensitivity, but all other known actions of alcohol require higher concentrations than this RPE action. (*Invest Ophthalmol Vis Sci.* 2000;41:2722–2729)

Since the original descriptions of the electro-oculogram (EOG) in humans,[1–4] intraretinal microelectrode recordings[5–10] have elucidated the underlying mechanisms. Light adaptation of the retina changes the quantity of an unknown substance or substances, probably produced by photoreceptors, that diffuses to the apical processes of the retinal pigment epithelium (RPE) where it binds to membrane-bound chemical receptors. These then liberate an intracellular second messenger that ultimately depolarizes the basolateral surface of the RPE cells, causing a light-induced increase in the corneofundal potential (hereafter termed light rise), by increasing the chloride conductance.[11] The external and internal transmitters are unknown, as is the relationship between the transmitter concentration and the stereotyped voltage changes. Thus, the time course of the concentration changes of the external or the internal transmitter may determine the timing of the light rise and the subsequent oscillations. The EOG remains a useful clinical test,[12–18] because it offers an overview of the functioning of photoreceptors, subretinal space, and RPE, but because light is used to provoke the voltage changes, retinal and RPE dysfunction cannot be separated. Therefore, other agents, such as bicarbonate ions, acetazolamide, and hyperosmotic solutions, which act directly on the RPE, have been investigated.[18–22] All have been found to cause a slow decrease in corneofundal potential.

Previous experiments[23–27] show that alcohol may cause a change similar to the light rise[28] and have related this to the generation of the c-wave, which is produced at the apical surface of the RPE. In contrast, in RPE preparations, alcohol in fairly high concentration acts on the apical surface to produce a basolateral increase in conductance.[28,29] We decided to reinvestigate the interactions of light and alcohol on the EOG, as a way (in humans) of determining more about the clinical implications of this test.

Methods

Subjects

Three students aged 20 to 25 years and the authors (seventh decade) gave informed consent, and the experimental protocols complied with the Helsinki declaration.

Recording Techniques

Five-millimeter chloride-coated silver disc electrodes were placed on each temple, near the lateral canthi, and a similar earth electrode was placed on the forehead. The recording was bitemporal (i.e., the voltages were generated by both eyes). Standard 30° horizontal eye movements were made at two per

From the Applied Vision Research Centre, Department of Optometry, City University London, United Kingdom.

Submitted for publication November 4, 1999; revised March 1 and April 14, 2000; accepted April 24, 2000.

Commercial relationships policy: N.

Corresponding author: Geoffrey B. Arden, Applied Vision Research Centre, Department of Optometry and Visual Science, City University, 311 Goswell Road, London EC1 V 7 DD, UK.
g.arden@city.ac.uk

Investigative Ophthalmology & Visual Science, August 2000, Vol. 41, No. 9

second. Voltages were amplified and displayed on a computer data acquisition system. The amplifier bandwidth was 1 to 100 Hz. Except when stated, the pupils were not dilated. Breath alcohol (BrAc) concentrations were measured with an alcometer (a portable, sensitive system based on fuel cell technology, and widely used in breath-testing motorists; model S400; Lion Laboratories, South Glamorgan, UK). The minimum detectable level is 0.01 mg/l of alveolar ethyl alcohol, which corresponds to a steady state arterial alcohol concentration of 23 mg/l, or 0.5 mM (manufacturer's calibration).

Stimuli

After the subjects had fasted 12 hours or more, ethyl alcohol was administered through three different routes: oral, intragastric, or intravenous. Usually, 100 ml of a 20% wt/vol mixture of alcohol and water was drunk in 10 seconds. In most experiments, the alcohol was obtained by diluting whisky containing 43% wt/vol ethyl alcohol. Larger and smaller quantities were used at the same dilution. After alcohol is consumed, any analysis of BrAc does not usually indicate blood alcohol for more than 30 minutes, because of the alcohol that remains in the mouth. If alcohol is retained in the mouth for 30 seconds (not swallowed), and then spat out, and the mouth is repeatedly (>20 times) rinsed with aliquots of water over 4 minutes, BrAc is zero. This procedure removes all residual alcohol from the upper gastrointestinal tract. In experiments to determine peak BrAc, this rinsing procedure was followed, and it is therefore considered that the values obtained from 7 to 15 minutes after ingestion indicated blood alcohol levels. To measure the initial rate of absorption into the bloodstream, we introduced alcohol either directly into the stomach through a nasogastric tube or by direct intravenous injection into a catheter. The catheter constantly delivered 1 ml/min 0.9% wt/vol saline into a forearm vein. Clinically pure ethyl alcohol, diluted to 10% wt/vol with sterile saline was injected at a rate of approximately 1 ml/sec.

Light intensities were measured with an electronic spot photometer (model LMT102; Lichtmesstechnik, Berlin, Germany). The subject viewed the white-painted walls of a small cubicle, lit to 50 candelas (cd)/m^2 by ceiling fluorescent lighting providing an approximate ganzfeld stimulus. The subjects had normally mobile pupils, diameter approximately 3 mm, so that the retinal illumination was 200 to 400 trolands (td). This nonstandard illumination was designed to cause a submaximal increase in light. For more intense light levels, pupils were dilated with 0.5% tropicamide drops, and retinal illumination was increased with photo floodlights, up to an approximate value of 10,000 td.

Results

Figure 1 compares the average effects of submaximal quantities of alcohol and light. Light and alcohol (administered orally, as described) both produced similar changes, except that the voltage increase caused by alcohol (termed the alcohol rise) peaked 2 to 3 minutes later than the light rise and the subsequent decrease in voltage also lagged the light response. Both alcohol and light produced similar damped oscillations in EOG voltage that continued for more than an hour,[24] but the changes after the first trough were not investigated quantitatively in this series of experiments. The mean ratio of the change peak-to-trough for alcohol was 2.0 and for light was 1.8. The effects of the combined stimuli are shown (Fig.1, squares) and compared with the sum of the separate light and alcohol responses (Fig. 1, continuous line). As the Discussion shows, the fact that the line ran through the squares, implying simple summation, was unexpected.

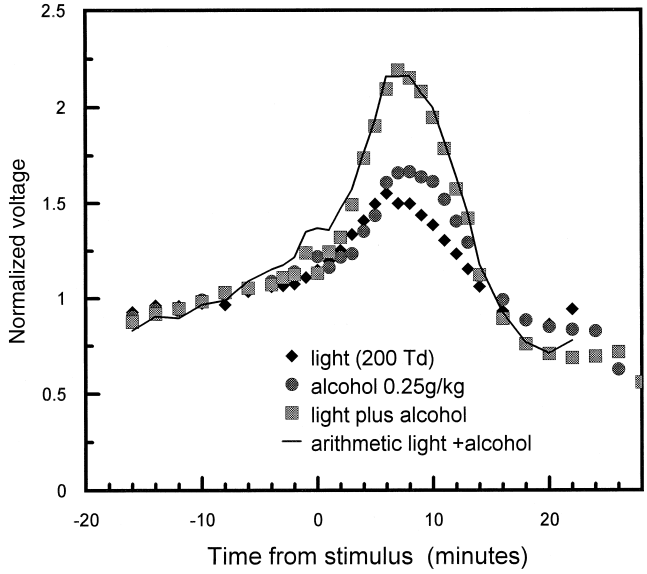

Figure 1. Change in EOG voltage with time: after 26 minutes of recording in darkness, or in increased illumination or with orally administered alcohol, or both. Average of five subjects' results. Time 0 is the time when experimental conditions changed. All the experiments were timed in the same way. To compare different experiments, the results from each subject were normalized by averaging all the voltages recorded between 11 and 26 minutes and expressing the subject's experimental results as a fraction of this average, thus avoiding any bias introduced if one subject's voltages were greater than another's. The SEM is smaller than the size of the points.

The Dose–Response Relationship for Oral Alcohol

Figure 2A shows a family of curves that illustrate the results of experiments on two subjects with differing doses of alcohol. Response amplitude increased with dose. For doses more than 9 mg/kg, the peak time did not vary with dose. The response as a fraction of the maximum is plotted against dose in Figure 2B. The highest alcohol dose produced a blood concentration below the legal maximum for driving in the United Kingdom (80 mg alcohol/100 ml blood). For the two lowest doses, the BrAc levels were below detection level (<0.5 mM in blood). Response saturation began at approximately 20 mg/kg. The data are consistent with the Naka–Rushton relationship,[30] but the saturation may in part have been due to a limitation in the rate of absorption of alcohol from the gut.

Time Course of Alcohol Responses: Relation to Blood Alcohol

Figure 3 shows alcohol concentration (when administered through a nasogastric tube) and voltage change as a function of time. No alcohol was measurable in the alveolar air until approximately 3 minutes after its injection into the stomach. There was no simple relationship between BrAc and RPE voltage. After its appearance in the pulmonary circulation, there

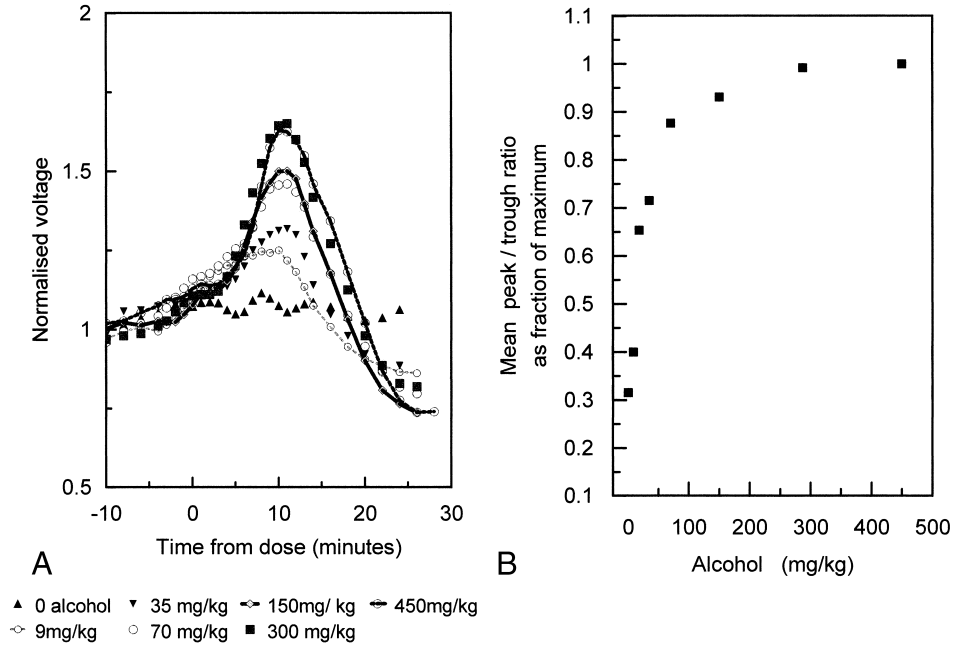

FIGURE 2. Dose–response relationship for alcohol administered orally. (**A**) Mean results for a series of dose levels, three-point smoothed. (**B**) Results expressed as V/V_{max}. The smallest dose producing a response (9 mg/kg) corresponds to 2.5 ml of standard-concentration whisky and produced a 30% maximal response. Results are the mean of experiments on two observers.

must be a transit time of approximately 15 to 20 seconds to the eye, and then alcohol has to reach its effector site at the RPE. The best fit between the light rise and alcohol rise in Figure 1 is obtained if the latter curve is advanced 3 minutes (the data were scaled for equal amplitudes), at which time the residual sum of differences between the two data sets is zero. Thus, the delay in the onset and peak of the alcohol rise compared with the light rise is accounted for by the delay in alcohol reaching the eye. When larger quantities of alcohol are ingested, the peak BrAc is delayed, and the decay is slowed, although the timing of the voltage changes is unaffected. A similar result is obtained with the light rise, which is a triggered response—that is, a brief period of stimulating light (2–3 minutes) causes an entire sequence of voltage changes almost identical with that occurring after a prolonged step of light.[2,3] Direct venous infusion of alcohol through a forearm venous catheter produces a brief increase in arterial alcohol, too short to provide full equilibration with the alveolar air. Figure 4 shows the effect of increasing doses of alcohol, injected in a few seconds, on BrAc and EOG voltage.

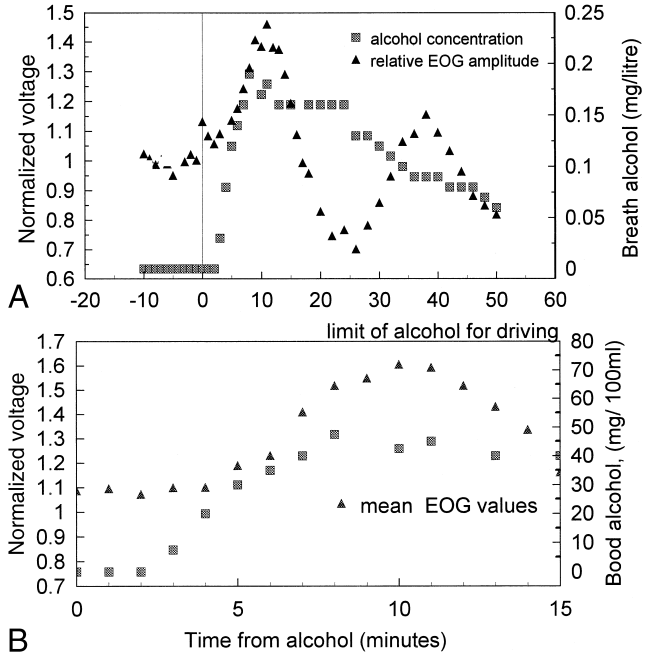

FIGURE 3. (**A**) Alcohol administered by intragastric tube, to enable observing voltage changes and breath alcohol changes early in the experiment. No BrAc was measurable before 3 minutes. Concentration increased, then declined before the first voltage peak, and continued to decrease as the voltage subsequently increased. (**B**) Expanded time base shows alcohol appeared first in alveolar air and later caused RPE changes. The *upper horizontal margin* of (**B**) represents legal upper limit of alcohol concentration for driving in the United Kingdom. Results are from a single experiment.

Alcohol (300 mg in 9 ml saline) injected into the venous line in 30 seconds caused an increase in voltage (data labeled 0.3 g in Fig. 4), although no BrAc could be detected. One gram (10% wt/vol alcohol in saline) was then injected in 10 seconds and later 3 g of 10% wt/vol alcohol was administered at the same rate. The maximum BrAc concentrations were 0.02 and 0.07 mg/l, respectively, reached after 30 seconds or less. BrAc for the 10-ml bolus declined below instrumental sensitivity after 1.5 minutes and for the 30-ml bolus after 4 minutes. The peaks developed in approximately 8 minutes and continued to develop long after breath alcohol could no longer be detected, reproducing the changes caused by a prolonged step of light (replotted from Fig. 1). The light rise appeared slightly sooner than that due to alcohol, but no allowance was made for the transit time of the alcohol between arm and eye.

Effect of Backgrounds

Figure 5A shows the effect of a background of light on the light response. Backgrounds of quite low luminance (L) greatly reduced the response. The effective stimulus seemed to be $\Delta L/L$. In addition, the time to peak of the light rise increased in the presence of a background. Similarly, after one dose of alcohol, a second produced a much smaller response, but it

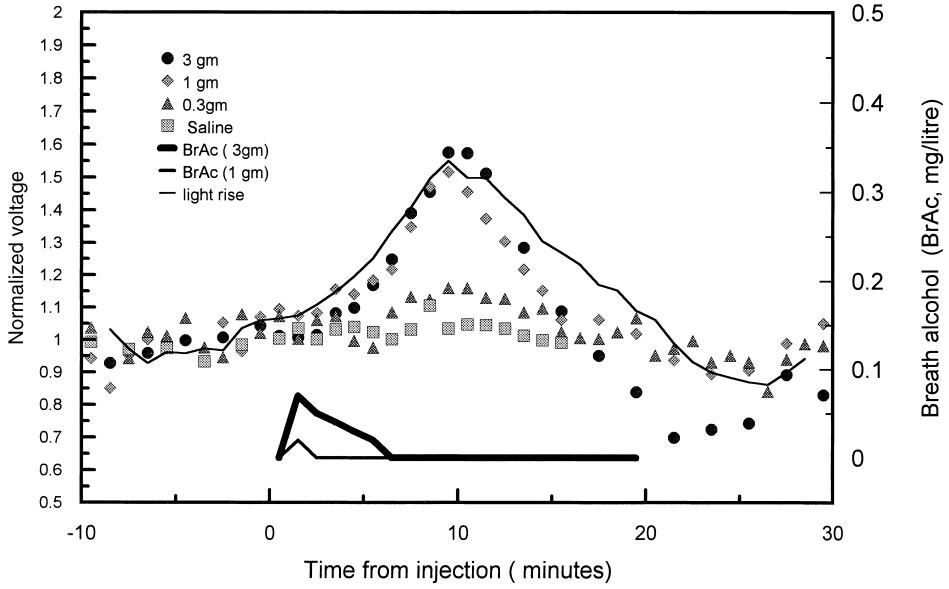

FIGURE 4. Intravenous alcohol injections and RPE voltage changes. The alcohol was provided as a bolus, which for the 0.3- and 1-g dose lasted 10 seconds and for the 3-g dose lasted 30 seconds. The timing and the duration of the alcohol rises are similar to the mean light rise from Figure 1 (*solid line*). Results are from a single experiment.

was difficult to maintain (in the fasting state) a constant level of breath alcohol on which another pulse could be superimposed. In Figure 5B a loading dose of 4 g was administered orally and induced a change in the EOG. Fifteen minutes later, the same dose administered at a time when the alcohol peak was declining has a negligible effect on the voltage change. After a further 43 minutes, when the potential seemed to have achieved a stable low value, a new dose (20 g) rapidly increased the BrAc. The EOG voltage increased, but to a smaller extent than the average (Fig. 5, circles, replotted from Fig. 1), and the time to the peak was delayed, as it was when light acted as a background to the light rise. Thus, a background of alcohol modified the effect of a pulse of alcohol on the RPE.

Figure 6 shows the effect of a background of light on the alcohol response (Fig. 6A) or vice versa (Fig. 6B). The alcohol response is scarcely affected by a background of light. Similarly, alcohol sufficient to cause symptoms of intoxication leaves the light response substantially unaffected.

Occlusion of Saturating Doses of Light and Alcohol

When the illumination was increased some 50-fold, and the alcohol dose was doubled (so that both agents produced maximal responses[2,3]; see Fig. 2), the response to the combined stimuli was little larger than the responses individually (Fig. 7). The peak-to-trough excursions for the alcohol were 2.58 and for light 2.55 (insignificantly different). The stimuli no longer summed linearly.

DISCUSSION

Alcohol and Light Produce Exactly the Same Sequence of EOG Changes

Administering alcohol by mouth, or as a brief intravenous bolus, produced a sequence of slow voltage changes that were markedly similar to those caused by a sudden step of light (after allowing for the delays in delivery of alcohol to the RPE). The current results extend those in previous work,[23–27] and it is difficult to avoid the conclusion (consistent with prior work) that both light and alcohol effects are caused by the same mechanism within the RPE, an increase in basolateral chloride conductance.[5–11,23,24,28,29,31] The light rise is evoked by brief illumination, but the possibility remained open that the timing of the voltage changes was determined by slow alteration in the concentration of the unknown light substance. Our results indicate that brief exposures to alcohol provoked the entire sequence, and the changes in conductance therefore seemed to be triggered in a stereotypical way by brief exposures to more than one agent. This is in agreement with the earlier suggestion that the light rise is mediated by intracellular second messengers,[10,23] and that RPE cells are also sensitive to alcohol.[29]

However, alcohol may provoke the production of the light substance within the retina, and for this reason we investigated the interaction of light and alcohol in the production of the voltage changes. We conclude that the results are inconsistent with the idea that the light substance is released by alcohol. Although alcohol present in the body reduces the effect of a second dose of alcohol, it does not affect the light response. In addition, as previously noted,[23] the alcohol effect is independent of the light level, although the action of light depends on previous retinal illumination. The voltage changes induced by submaximal doses of light and alcohol were simply summed, although those of larger doses were occluded, which implies a final common pathway for these agents. It is noteworthy that the effect of pulses of light and pulses of alcohol had the same effect as those of prolonged exposures. This implies that some part of the chain of reactions between the provoking agent and the final conductance change became insensitive to further stimulation soon after the reactions began. However, the effects of alcohol and light were summed, although the agents were not administered synchronously (i.e., the summation occurred after the desensitization).

The Simplest Model to Explain the Results

Although our experiments in humans cannot advance knowledge of the cellular mechanisms involved in the production of the voltage changes,[32] the results directly lead to the conclu-

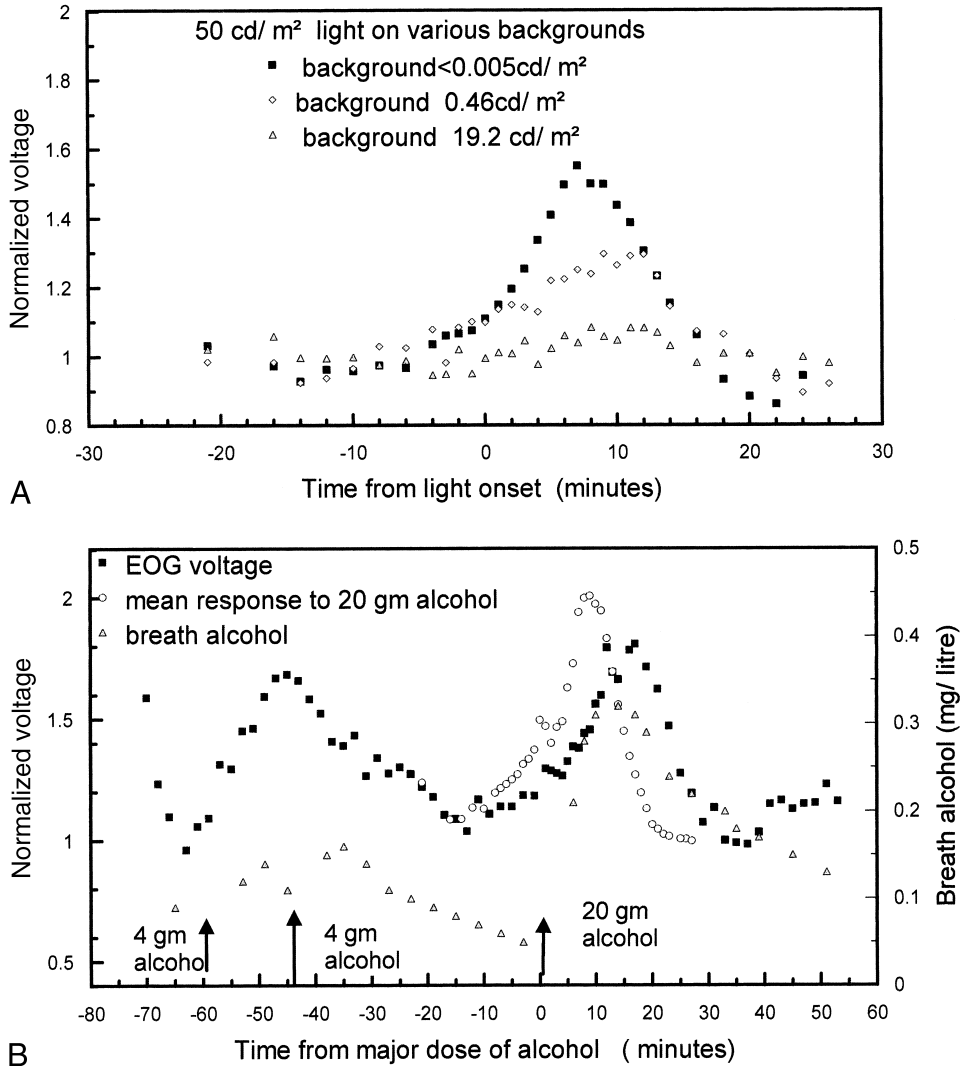

Figure 5. (**A**) Effect of background light on the light rise and (**B**) of alcohol on the alcohol rise. These latter experiments had to be performed in fasting subjects, and therefore it was impossible to maintain a constant background alcohol level. Four grams alcohol produced a large response initially, but very little change was evoked by a similar dose administered when blood alcohol was elevated. After blood alcohol had decreased, a large dose produced a smaller response than without alcohol (the mean curve from Fig. 1, ○). In the presence of alcohol (or light) the reduced response to a subsequent dose peaked at a later time than normal. Mean of experiments on two different observers.

sion embodied in the diagram of Figure 8, which is derived from Steinberg et al.[10]

The light substance binds to apical membrane receptors and activates an intracellular second messenger. This acts on some intracellular machinery that causes the change in conductance. This machinery, as argued earlier, is responsible for the time course of the light rise of the EOG. We further suppose that alcohol also binds to different molecules on the RPE membrane. These could be particular regions of molecules linked to second receptor systems.[33–36] However, this is not essential to the hypothesis, and alcohol may act by modulating the activity of any of the ligand- or voltage-gated channels, pumps, or cotransporters that have been described in the RPE membrane[33] or by a direct intracellular action.

Thus, the point at which alcohol enters the system is indeterminate; several possible routes are indicated in Figure 8.

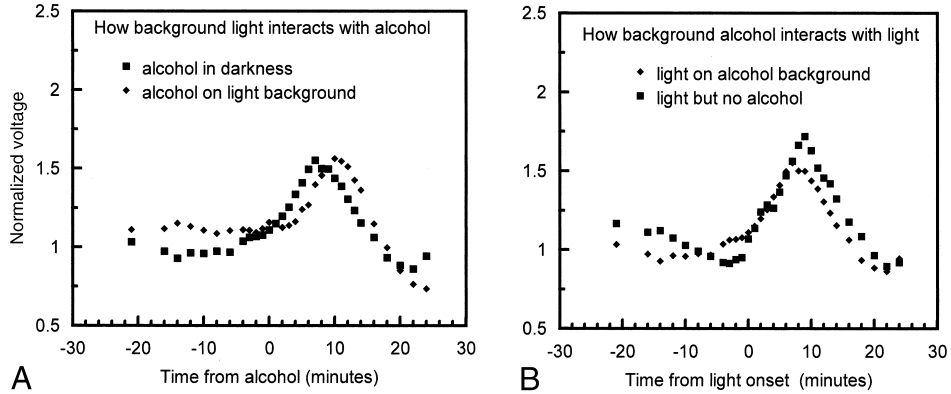

Figure 6. (**A**) Effect of alcohol in darkness compared with the response at 200 td. (**B**) Effect of light without alcohol or after 20 g alcohol administered after eating (to produce a prolonged stable alcohol level in the blood). Mean of experiments on two observers.

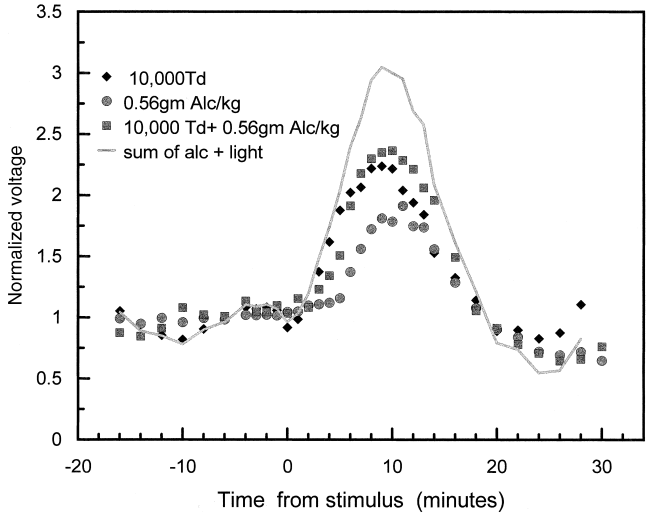

FIGURE 7. Intense light and large doses of alcohol did not sum. Compare with Figure 1. Mean of experiments on two observers.

The diagram illustrates that alcohol indirectly operates the same intracellular machinery as light and this is the final common pathway that saturates when the light is intense and the alcohol dose high. The model makes strong predictions that can be tested experimentally—for example, that various other substances known to affect the transepithelial potential (TEP) should interact, in animal preparations, with light and alcohol and produce voltage changes with a predictable time course. A model that locates the site where alcohol acts within the retina, causing liberation of a second messenger that is specific for alcohol, and acts on the RPE independently of the light substance (although with similar kinetics and desensitization characteristics) must be considerably more complex than Figure 8 indicates.

Mechanisms of Action of Alcohol

There is an extensive body of literature on the mechanisms whereby alcohol can affect ionic conductances and other cellular mechanisms (see recent reviews[33–36]). The present results demonstrate that the change in EOG voltage required less alcohol than used in almost all investigations, and future experiments on the RPE could thus utilize low concentrations of alcohol that would not excite a range of other cellular mechanisms. The effective tissue concentration of alcohol in our experiments is difficult to estimate. The total dose is not simply distributed through the body or through the blood. Alcohol is destroyed in the gut and liver before it reaches the systemic circulation, and as soon as it leaves the capillaries (to an unknown extent at each passage), it is metabolized in the tissues. Furthermore, oral alcohol triggers an RPE response much before the peak concentration develops. The semisaturation oral dose is approximately 20 mg/kg (approximately 5 ml of whisky) but the process has been triggered before most of the dose has appeared in the blood. A dose of 0.3 g delivered intravenously produces an effect. If the simplistic assumption is made that the active tissue concentration is the total dose in 5 l (of blood) the resultant concentration is approximately 1 millimole. The concentrations used in experiments on the acute affect of alcohol on various channels or ionic transport mechanisms are much higher. Examples are the γ-aminobutyric acid (GABA) receptor Cl^- channels,[27–41] glycine receptors,[42] the inositol 1,2,5, triphosphate receptor,[43,44] the *N*-methyl D-aspartate (NMDA) or glutamate receptor cation channels (in reports that indicate specific alcohol sensitivities[45–49]), voltage-gated Ca^{2+} channels[48–52] or other channels conducting sodium.[53–54] Such channels are affected by approximately 5 to 200 mM alcohol, with the usual lower level of approximately 30 mM. Alcohol also acts on second-messenger systems at concentrations of 30 to 300 mM,[43] much above the levels used in this experiment. In intact cells, the activity of the IP_3 signaling pathway is affected by concentrations of alcohol as low as 20 mM (for a review see Reference 44).

There have been only a few comparable studies of the direct effect of alcohol on the basal membrane of the RPE.[25,26–29] Direct measurement of the effect of alcohol on the isolated RPE[25–26] has shown that alcohol (in 30- and 125-mM concentrations) is more effective when applied to the apical surface of the RPE but affects the basal chloride conductance. In other experiments on the effects of nonsteroidal anti-inflammatory drugs (NSAIDs) on the RPE, the substances were dissolved in 20 mM alcohol. Although this was thought to be an inactive concentration, control experiments showed a small effect of the alcohol itself.[29]

Agents Affecting the RPE

Cyclic adenosine monophosphate (cAMP), adenosine, dopamine, and melatonin[30,31,57–63] modify the basolateral chloride conductance at micromolar concentration and evoke changes with a time course similar to that of the light rise. However, their detailed actions are different. Adenosine and dopamine and some NSAIDs produce increases of TEP similar to the light rise, but also (unlike alcohol) abolish the light rise, whereas melatonin hyperpolarizes the basal membrane and reduces

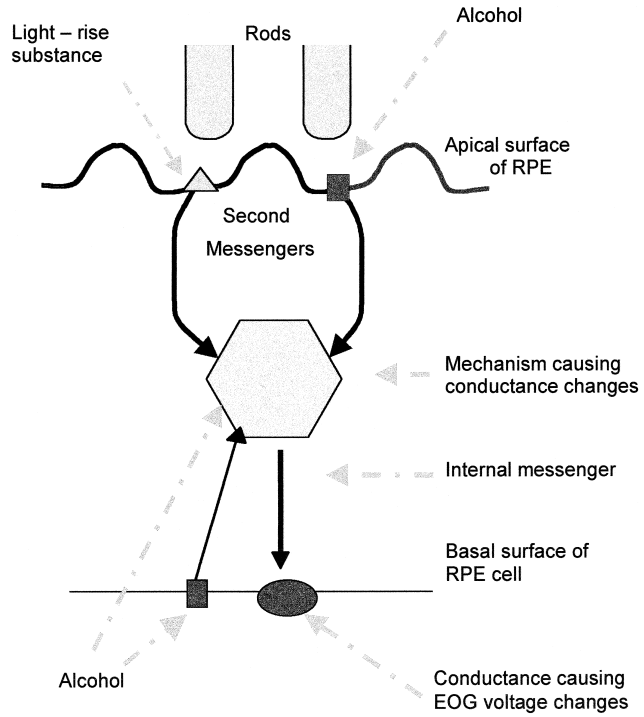

FIGURE 8. Diagram illustrating pathways by which light and alcohol affect the RPE.

TEP.[28,29,31,57–62] The similarity of the time course of the responses to amines and the effects of light have not been commented on, but because the voltages and resistances change slowly, it is plausible to suggest that several of these agents as well as alcohol may act indirectly on the conductances they control.

Clinical Implications for the EOG

The clinical value of the EOG is limited in that changes in voltage are unrelated to retinal function, and the conductance changes have not been directly related to known transport through the RPE, although they are thought to be indicators of its occurrence.[29,32] However, comparing the light rise with the alcohol effect may determine, by a simple noninvasive test, whether parts of the intracellular machinery (indicated in Fig. 8 by the hexagon and the basal conductances) are operative, even when the retina is nonfunctional—for example, after receptors die. Cases of possible interest would be certain inherited abnormalities of the RPE[28] both in animals and in patients with various conditions (e.g., retinitis pigmentosa[63]), in whom damage to photoreceptors may secondarily cause atrophic changes in the RPE such as has been demonstrated in an animal model.[64]

Acknowledgments

The authors thank Sven-Eric Nilsson for suggesting these experiments; Christopher R. Hogg and Eugene Sainsbury for a variety of technical support; John Lawrenson for the loan of MacLab; Lyon Laboratories for the alcometer; and Polly C. Falk, for supervising the intravenous infusions.

References

1. Kris C. Corneo-fundal potential variations during light and dark adaptation. *Nature*. 1958;182:1027–1028.
2. Arden GB, Kelsey JH. Changes produced by light in the standing potential of the human eye. *J Physiol.* 1962;161:189–204.
3. Arden GB, Kelsey JH. Some observations on the relationship between the standing potential of the human eye and the bleaching and regeneration of visual purple. *J Physiol.* 1962;161:205–226.
4. Arden GB, Barrada A. An analysis of the electro-oculograms of a series of normal subjects. *Br J Ophthalmol.* 1962;46:468–482.
5. Linsenmeier RA, Steinberg RH. Origin and sensitivity of the light peak of the intact cat eye. *J Physiol.* 1982;331:653–673.
6. Miller SS, Edelman DJ. Active ion transport pathways in the bovine retinal pigment epithelium. *J Physiol.* 1990;424:283–300.
7. Miller SS, Lin H. $[K+]_o$-induced changes in apical membrane voltage modulate pH in frog retinal pigment epithelium. *Invest Ophthalmol Vis Sci.* 1989;30(4):**S**168.
8. Miller SS, Steinberg RA. Active transport of ions across the frog retinal pigment epithelium. *Exp Eye Res.* 1977;25:235–248.
9. Steinberg RH, Linsenmeier RA, Griff ER. Retinal pigment epithelial cell contributions to the electroretinogram and electrooculogram. In: Osbourne NN, Chader GJ, eds. *Progress in Retinal Research*. Vol. 4. New York: Pergamon; 1985:33–66.
10. Steinberg RH, Linsenmeier RA, Griff, ER. Three light evoked responses of the pigmented epithelium. *Vision Res.* 1983;231:315–323.
11. Gallemore RP, Steinberg RH. Effect of DIDS on the chick retinal pigment epithelium, II: mechanism of the light peak and other responses originating at the basal membrane. *J Neurosci.* 1984;9:1977–1989.
12. Kolder H. Electro-oculography. In: Heckenlively J, Arden GB, eds. *Principles and Practice of Clinical Electrophysiology of Vision.* St. Louis: Mosby Year Book; 1989:310–313.
13. Stavrou P, Good PA, Broadhurst EJ, Bundey S, Fielder AR, Crews SJ. ERG and EOG abnormalities in carriers of X- linked retinitis pigmentosa. *Eye.* 1996;10:581–589.
14. Pinckers A, Cuypers MH, Aandekerk AL. The EOG in Best's disease and dominant cystoid macular dystrophy (DCMD). *Ophthalmic Genet.* 1996;17:103–108.
15. Miyake Y, Horiguchi M, Suzuki S, Kondo M, Tanikawa A. Electrophysiological findings in patients with Oguchi's disease. *Jpn J Ophthalmol.* 1996;40:511–519.
16. Marmor MF, McNamara JA. Pattern dystrophy of the retinal pigment epithelium and geographic atrophy of the macula. *Am J Ophthalmol.* 1996;122:382–392.
17. O'Brien C, Duvall–Young J, Brown M, Short C, Bone M. Electrophysiology of type 2 mesangiocapillary glomerulonephritis with associated fundus abnormalities. *Br J Ophthalmol.* 1993;77:778–780.
18. Gupta LY, Marmor MF. Sequential recording of photic and non photic electro-oculogram responses in patients with extensive extramacular drusen. *Doc Ophthalmol.* 1994;88:49–55.
19. Madachi–Yamamoto S, Yonemura D, Kawasaki K. Diamox response of ocular standing potential as a clinical test for retinal pigment epithelial activity. *Acta Soc Ophthalmol Jpn.* 1984;88:1267–1272.
20. Madachi–Yamamoto S, Yonemura D, Kawasaki K. Hyperosmolarity response of ocular standing potential as a clinical test for retinal pigment epithelial activity. *Doc Ophthalmol.* 1984;57:153- 262.
21. Segawa Y, Shirao Y, Kawasaki K. Retinal pigment epithelial origin of bicarbonate response. *Jpn J Ophthalmol.* 1997;41:231–234.
22. Yonemura D, Kawasaki K, Madachi–Yamamoto S. Hyperosmolarity response of ocular standing potential as a clinical response for retinal pigment epithelium activity. Choroidal dystrophies. *Doc Ophthalmol.* 1984;57:163–73.
23. Skoog KO, Textorius O, Nilsson SE. Effects of ethyl alcohol on the directly recorded standing potential of the human eye. *Acta Ophthalmol* (*Copenh*). 1975;53:710–720.
24. Skoog KO. The c-wave of the human DC registered ERG, III: effect of ethyl alcohol on the c-wave. *Acta Ophthalmol* (*Copenh*). 1974;52:1–11.
25. Pautler EL, Beezley D. The potentiating effect of ethanol on the blue light depolarisation of the retinal pigment epithelium. *Alcohol Clin Exp Res.* 1990;14:761–765.
26. Pautler EL. Photosensitivity of the isolated pigment epithelium and arachidonic acid metabolism. *Curr Eye Res.* 1994;13:687–695.
27. Zrenner E, Riedel KG, Adamczyk R, Gilg T, Liebhardt E. Effect of ethyl alcohol on the electrooculogram and color vision. *Doc Ophthalmol.* 1986;63:305–312.
28. Gallemore RP, Maruiwa F, Marmor MF. Clinical electrophysiology of the retinal pigment epithelium. In: Wolfenburger A, Marmor MF, eds. *The Retinal Pigment Epithelium.* Oxford, UK: Oxford University Press; 1998:199–123.
29. Bialek S, Quong JH, Yu K, Miller SS. Non-steroidal anti-inflammatory drugs alter chloride and fluid transport in bovine retinal pigment epithelium. *Am J Physiol.* 1996;C1175–C1189.
30. Naka K, Rushton WAH. The generation and spread of S-potentials in fish (Cyprinidae). *J Physiol* (*Lond*). 1970;192:437–461.
31. Gallemore RP, Hughes BA, Miller SS. Light induced responses of the retinal pigment epithelium. In: Wolfenburger A, Marmor MF, eds. *The Retinal Pigment Epithelium*. Oxford, UK: Oxford University Press; 1998:175–199.
32. Hughes BA, Gallemore RP, Miller SS. Transport mechanisms in the retinal pigment epithelium. In: Wolfenburger A, Marmor MF, eds. In*: The Retinal Pigment Epithelium*. Oxford, UK: Oxford University Press; 1998:103–134.
33. Fitzgerald LW, Nestler EJ. Molecular and cellular adaptations in signal transduction pathways following ethanol exposure. *Clin Neurosci.* 1995;5:165–713.
34. Crews FT, Morrow AL, Criswell H, Breese G. Effects of ethanol on ion channels. *Int Rev Neurobiol.* 1996;39:283–367.
35. Lovinger DM. Alcohols and neurotransmitter gated ion channels: past, present and future. *Naunym Schmeideburgs Arch Pharmacol.* 1997;356:267–282.
36. Pandy SC. Neuronal signalling systems and ethanol dependence. *Mol Neurobiol.* 1998;17:1–13.
37. Yeh HH, Kolb JK. Ethanol modulation of GABA-activated current responses in acutely dissociated retinal bipolar cells and ganglion cells. *Alcohol Clin Exp Res.* 1997;21:647–655.

38. Harris RA, Mihic SJ, Brozowski S, Hadingham K, Whiting PJ. Ethanol flunitrazepam and pentobarbital modulation of GABA A receptors in mammalian cells and *Xenopus* oocytes. *Alcohol Clin Exp Res.* 1997;21:444–451.
39. Soldo BL, Proctor WR, Dunwiddie TV. Ethanol differentially modulates GABA A receptor mediated chloride currents in hippocampal, cortical and septal neurons in rat brain slices. *Synapse.* 1994; 2:94–103.
40. Harris RA, Proctor WR, McQuilkin SJ, et al. Ethanol increases GABA-A responses in cells stably transaffected with receptor subunits. *Alcohol Clin Exp Res.* 1995;19:226–232.
41. Suzdak PD, Schwartz RD, Skolnick P, Paul SM. Alcohols stimulate gamma-aminobutyric acid receptor-mediated chloride uptake in brain vesicles: correlation with intoxication potency. *Brain Res.* 1988;444:340–345.
42. Valenzuela CF, Cardoso RA, Wick MJ, Weiner JL, Dunwiddie TV, Harris RA. Effects of ethanol on recombinant glycine receptors expressed in mammalian cell lines. *Alcohol Clin Exp Res.* 1998; 22:1132–1136.
43. Renard-Rooney DC, Seitz MR, Thamas AP. Inhibition of hepatic inositol 1,2,5,-triphosphate receptor function by ethanol and other short chain alcohols. *Cell Calcium.* 1997;5:387–398.
44. Hoek JB, Rubin E. Alcohol and membrane-associated signal transduction. *Alcohol Alcohol.* 1990:25;143–156.
45. Anders DL, Blevins T, Sutton G, Chandler LJ, Woodward JJ. Effects of c-Src tyrosine kinase on ethanol sensitivity of recombinant NMDA receptors expressed in HEK 293 cells. *Alcohol Clin Exp Res.* 1999;23:357–362.
46. Mirshahi T, Anders DL, Ronald KM, Woodward JJ. Intracellular calcium enhances the ethanol sensitivity of NMDA receptors through an interaction with the C0 domain of the NR1 subunit. *Neurochemistry.* 1998;71:1095–1107.
47. Weight FF, Peoples RW, Wright JM, Lovinger DM, White G. Ethanol action on excitatory amino acid activated ion channels. *Alcohol Alcohol*. 1993;(suppl 2)28:353–358.
48. Michaelis ML, Michaelis EK. Effects of ethanol on NMDA receptors in brain: possibilities for Mg(2+)-ethanol interactions. *Alcohol Clin Exp Res.* 1994;18:1069–1075.
49. Chu B, Anatharam V, Treistman SN. Ethanol inhibition of recombinant heteromeric NMDA channels in the presence and absence of modulators. *Neurochemistry.* 1995;65:240–248.
50. Brodie MS, McElvain MA, Bunney EB, Appel SB. Pharmacological reduction of small conductance calcium activated potassium current (SK) potentiates the excitatory effect of alcohol on ventral tegmental area dopaminergic neurons. *Pharmacol Exp Ther.* 1999;290:325–333.
51. Twombly DA, Herman MD, Kye CH, Narahashi T. Ethanol effects on two types of voltage activated calcium channels. *J Pharmacol Exp Ther.* 1990;254:1029–1037.
52. Mullikin–Kilpatrick D, Treisman SN. Electrophysiological studies on calcium channels in naïve and ethanol-treated PC 12 cells. *Alcohol Alcohol.* 1993;28(suppl 2):385–390.
53. Tachibana I, Okabayashi Y, Akiyama T, Koide M, Matsushita K, Otsuki M. Ethanol inhibits CCK-induced enzyme secretion by affecting calcium pump activities in isolated rat pancreatic islets. *Pancreas.* 1996;13:316–323.
54. Dopico AM, Lemos JR, Treistman SN. Ethanol increases the activity of large conductance Ca(2+)-activated K+ channels in isolated neurohypophysial terminals. *Mol Pharmacol.* 1996;49:40–48.
55. Li C, Aguayo L, Peoples RW, Weight FF. Ethanol inhibits a neuronal ATP-gated ion channel. *Mol Pharmacol.* 1993;44:871–875.
56. Weight FF, Li C, Peoples RW. Alcohol action on membrane ion channels gated by extracellular ATP (P2X) receptors. *Neurochem Int.* 1999;35:143–152.
57. Kuntz CA, Crook RB, Dimitriev A, Steinberg RH. Modification by cyclic adenosine monophosphate of basolateral membrane chloride conductances in chick retinal pigment epithelium. *Invest Ophthalmol Vis Sci.* 1994;35:422–433.
58. Gallemore RP, Steinberg RH. Effects of dopamine on the chick retinal pigment epithelium: membrane potentials and light evoked responses. *Invest Ophthalmol Vis Sci.* 1990;31:67–80.
59. Maruiwa F, Nao-I N, Nakazaki S, Sawada A. Effects of adenosine on chick retinal pigment epithelium: membrane potentials and light evoked responses. *Curr Eye Res.* 1995;14:685–691.
60. Dawis SM, Neimeyer G. Dopamine influences the light peak in the perfused mammalian eye. *Invest Ophthalmol Vis Sci.* 1986;27: 330–335.
61. Dawis SM, Neimeyer G. Similarity and diversity of monoamines in their effects on the standing potential, light peak and electroretinogram of the perfused cat eye. *Clin Vision Sci.* 1988;3:109–118.
62. Nao-I N, Nilsson S-E, Gallemore RP, Steinberg RH. Effects of melatonin on the chick retinal pigment epithelium: membrane potentials and light-evoked responses. *Exp Eye Res.* 1989;49:573–589.
63. Arden GB, Wolf JE. The electrooculographic responses to alcohol and light in a series of patients with retinitis pigmentosa. *Invest Ophthalmol Vis Sci*. 2000;41;0000–0000.
64. Strauss O, Wiederholt M, Weinrich M. Activation of Cl^- currents in cultured rat retinal pigment epithelial cells by intracellular applications of inositol-1,4,5-triphosphate: differences between rats with retinal dystrophy (RCS) and normal rats. *J Membr Biol.* 1996;151:189–200.