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Zebrafish electroretinogram responses

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Abstract

The electroretinogram (ERG) is a commonly used method to investigate the visual system in both clinical and scientific settings to study the neurotransmission of the retina and to measure the light responsivity of cells in the retina. Zebrafish are quickly becoming an ideal model organism for studying the visual system due to their utilization of cone dominated vision and their similar spectral sensitives to humans. Dr. Renna's lab has designed an *ex-vivo* ERG system with less electrical interference, creating defined electrical responses from mouse retinae. The setup allows for continual perfusion of the retinal tissue with chemical blockers to isolate specific components of the light response. The objective was to resolve any issues that occurred when transiting from a mice ERG protocol to a zebrafish ERG protocol, and to obtain light responses from zebrafish retinae in differing light intensities. An *ex-vivo* ERG can be conducted on zebrafish retinae, a light response can be obtained, and a concise protocol can be created for zebrafish ERGs. Through determining if a light response can be obtained, future study of the zebrafish visual system can be conducted, as ERGs can be conducted on zebrafish to study different genetic zebrafish lines and zebrafish specific photoreceptor responses, such as those from rods and cones.

Introduction

The electroretinogram, or ERG, is a useful method to investigate the visual system and the zebrafish is an ideal model organism with a highly similar visual system to humans, making zebrafish ERGs vastly important in the field of electrophysiology. The visual system of a zebrafish contains, in order from the proximal end of the retina to the distal end of the retina: ganglion cells, amacrine cells, bipolar cells, horizontal cells, photoreceptors, and retinal pigment

epithelium, or RPE (Hill et al., 2022). The photoreceptors, which consist of rods and cones, are the point of main focus in the experiments detailed in this paper. In the adult zebrafish retina, there are one rod type and four cone types, with the rod's main function in the retina mediating vision in low-light and monochromatic conditions, and with the cone's main function mediating vision in bright light and providing color information (Hill et al., 2022). The transduction pathway of the visual system in zebrafish begins with light being captured by the opsins, which are cone photopigments, and rhodopsin, which is rod photopigment, on the photoreceptors in the back of the retina (Hill et al., 2022). When light enters the eye, it causes an activation cascade by activating rhodopsin which then activates transduction, a G protein, which then activates cGMP phosphodiesterase (PDE) (Hill et al., 2022). The cGMP PDE catalyzes the breakdown of cGMP to 5'-GMP and as the cGMP concentration decreases in the retina, it detaches from the cGMP-sensitive cation channels that are permeable to both sodium ions (Na^+) and calcium ions (Ca^{2+}), resulting in the closure of these channels, leading to reduced sodium and calcium influx (Hill et al., 2022). The retina is unique in its physiology as depolarization occurs in the dark due to the opening of the cation channels, while hyperpolarization occurs in the light due to the closure of the cation channels (Hill et al., 2022). The hyperpolarization causes photoreceptors to stop the release of glutamate, which disinhibits the bipolar cells, depolarizing them (Hill et al., 2022). These excited bipolar cells then release neurotransmitters (e.g. glutamate) onto the ganglion cells, which also depolarize and generate action potentials. The action potentials are sent to the central nervous system via the optic nerve (Hill et al., 2022). The visual system in zebrafish and humans are very similar and follow a near-identical transduction pathway, allowing studies about vision and its cellular components to be studied in depth.

Zebrafish are quickly becoming an ideal model organism for studying the visual system. First, they are easy to breed, due to short generation times, and to maintain, with a low cost of maintenance even for large numbers of zebrafish (Richardson et al., 2017). Due to their short generation times, zebrafish also have a high rate of retinogenesis, with the major retinal cell types differentiated and connected to their brain targets by 72 hours post fertilization (Jaroszyunska et al., 2021). Secondly, 84% of known human disease-causing genes have at least one zebrafish orthologue (Richardson et al., 2017). Zebrafish orthologues make the studying and application of causes and treatments of specific human diseases readily accessible. Thirdly, zebrafish have cone-dominated vision and similar spectral sensitivities to humans as well as similar genes (Jaroszyunska et al., 2021). Finally, zebrafish genes are highly versatile and can be easily manipulated in order to study different genetic zebrafish lines (Richardson et al., 2017). Overall, zebrafish are an ideal model organism for ERGs and the investigation of the visual system.

The type of ERG that is performed in the experiments detailed in this paper is the full-field ERG or the Ganzfeld stimulation. In a full-field ERG flashes the entire retina is illuminated with a uniform light for a duration of only a few milliseconds, during which time voltage difference across the retina is measured with electrodes placed above and below the retina (Whatham et al., 2017). The retina can be light or dark adapted and be *ex-vivo* or *in-vivo* (Whatham et al., 2017). The ERG system used in this study is an *ex-vivo* system which allows for the responses of isolated retinal tissues outside of the zebrafish's body to be directly examined in response to differing light intensities, while mimicking the natural environment of the retina.

The ERG response has multiple areas of interest within the responses that are produced. One area of interest is the isolation of specific waves, the A and B waves, within the ERG response. There is another wave present in the retina, a C wave, which is a long positive wave that occurs after the B wave, and originates in the RPE of the retina (Vinberg & Kefalov 2015). Due to the *ex-vivo* ERG that is performed, the dissection techniques remove the RPE on the retina and efficiently eliminate the C wave from ERG recordings. When the C wave is removed from the recordings, a slow, negative PIII component instead presents, which is thought to originate from the Müller glia cells in the retina (Vinberg & Kefalov 2015). In order to isolate the A and B waves, which originate due to activities in the photoreceptors and ON bipolar cells, respectively, two different pharmacological agents are used (Vinberg & Kefalov 2015). The isolation of the B wave occurs through the addition of Barium Chloride (BaCl), while the isolation of the A wave occurred through the addition of BaCl and DL-AP4 in dark-adapted mice retina ERG responses (Vinberg & Kefalov 2015). The isolation of these waveforms provides information about specific retinal cell types, such as the photoreceptors and bipolar cells. The isolation of the A and B waveforms is also possible in zebrafish *ex-vivo* ERGs.

Materials and Methods

Ethical Approval

Animal use protocols were approved by Institutional Animal Care and Use Committee at the University of Akron.

ERG Initial Setup

The ERG rig used in Dr. Renna's lab consists of an upright microscope, gravity fed perfusion system, inline temperature control unit, recording and reference electrodes, LED light source unit, faraday cage, headstage detect, amplifier, digitizer, and computer. Since the experiments were performed in the dark, any lights that were present on the machines or computers were covered in blackout tape or red film. To begin setting up the ERG for an experiment, Locke's solution was first made. The solution was stirred, and the pH was brought to 7.50 using about 20 drops of 5M NaOH. The 1000 mL of Locke's solution was divided into three 500 mL Pyrex bottles with 300 mL of Locke's solution in two bottles and 150 mL in one bottle. The remaining 250 mL of Locke's solution was poured into two petri dishes, one labeled for dissection, and one labeled for dual retina chamber setup. At this point, the computer, amplifier, digitizer, and LED light source were turned on for the ERG rig. After this setup for an experiment, the zebrafish that would be used were collected. The full ERG rig and pictures of the setup can be found in Matthew Tarchick and Paul Bonezzi's paper (Bonezzi et al., 2020).

Animals

Animals used in this experiment were *Danio rerio*, commonly known as zebrafish (Figure 1). Zebrafish were housed in a tank within a room on a 12-hour dark and 12-hour light cycle and dark adapted for at least 6 hours before experiments. Zebrafish were obtained from the holding tank and transported in a closed container which did not allow any light to pass through. After the zebrafish were transported from the holding room, they were taken into the dark ERG room while alive. Zebrafish were sacrificed using anesthesia and decapitation. The zebrafish were placed into a labeled anesthesia petri dish that contained the anesthesia solution until they

stopped moving and breathing. Anesthesia solution consisted of 100 mL of deionized (DI) water, 0.5 g of MS-222, and 1.0 g of sodium bicarbonate, then the pH was taken to verify it was at 7.00. The time from collection of the zebrafish to death was on average about 1 hour and 15 minutes. After the fish were determined to be fully anesthetized in the anesthesia solution by monitoring for breathing or gill movement, and by squeezing the tail of the fish with tweezers to monitor for any movement, the fish were then placed into a labeled dissection Petri dish filled with Locke's solution and decapitation was performed.

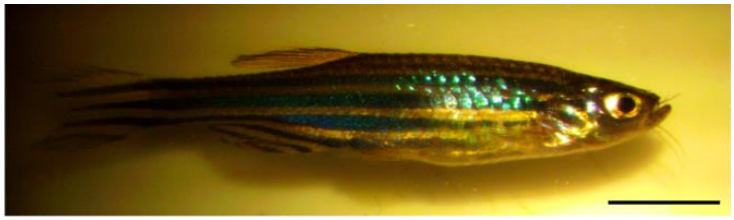

Figure 1. *Danio rerio,* also commonly known as a zebrafish. Black scale bar is 5 mm.

Dissection

After the zebrafish were sacrificed their retinae were isolated via dissection. The dissection was modeled after a mice retinae dissection; however, changes were made to the protocol due to the zebrafish retinae presenting differently and being much smaller than mice retinae. The dissections were performed in a dim-red LED light microscope in order to maintain the dark adaptation of the zebrafish and to minimize photobleaching of the retinae as much as possible. The labeled dissection Petri dish was filled with Locke's solution with continuous 95% O_2 and 5% CO_2 perfused through the Locke's solution during dissection. The eyes of the zebrafish were removed from the head (Figure 2), and one was placed onto a cotton ball within the dissecting Petri dish that was soaked with Locke's solution. A small cut was made into one eye using a needle, then micro scissors were used to open the cut across the front of the eye in a

circular motion. The eyeball was then placed back into the Locke's solution and the lens, vitreous, and other visual structures were removed from the retina. The retina was then successfully isolated, and the same process was repeated with the other eyeball (Figure 3). After the retinae were both isolated, the body and head of the zebrafish were properly disposed of according to the animal use protocol. The time of dissection of two retinae from one zebrafish was on average 15 minutes. The retinae were almost always completely intact and any RPE was removed as much as possible without damaging the retinae.

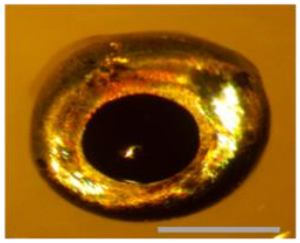

Figure 2. Isolated eyeball from zebrafish. White scale bar is 1 mm.

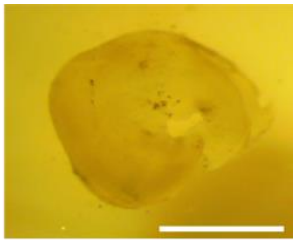

Figure 3. Isolated retina from zebrafish. White scale bar is 1 mm.

Dual Retina Chamber Setup

In order to measure the response of the retinae to light, the retinae were mounted onto an enclosed dual retina chamber after they were dissected from the zebrafish, which allowed two retinae's responses to stimuli to be examined at one time. The dual retina chamber, shown in Figure 4, was created by Matthew Tarchick, a graduate student in Dr. Renna's lab, and was 3D-printed specifically for zebrafish retinae. Before the zebrafish were collected, the chamber was

set up by placing four electrodes into the chamber. The chamber was completely submerged in Locke's solution to be able to flush out any bubbles in the chamber, which could impact recording results. A syringe was used to push Locke's solution into each of the electrode slots in the chamber and once the bubbles were removed, the electrodes were placed into the chamber. The chamber was then brought out of the Locke's solution and a stadium was used to cover the mounting area for the retinae. The Locke's solution was then pipetted into the stadium until filled. Once the retinae were isolated the chamber was then used to mount the retinae for the ERG. The retinae were pipetted out of the dissection dish and transported into the Locke's solution in the stadium. Under a microscope, the retinae were guided on top of the mounting area with tweezers and laid flat. The Locke's solution was then pipetted out of the stadium and the stadium was removed. The top portion of the chamber was then screwed on and the whole chamber was placed into the ERG rig. The chamber was secured in the ERG rig through the electrodes which were securely inserted into the headstage detect.

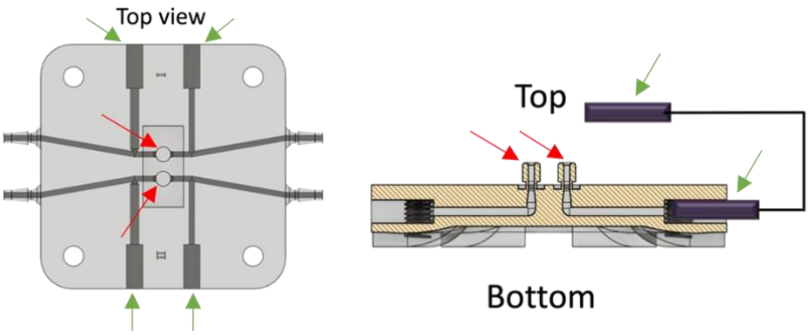

Figure 4. Custom 3D-printed ERG chamber used to mount retinae. This schema and 3D design was created by Matthew Tarchick, a graduate student in Dr. Renna's Lab. The retinae would be placed at the red arrows and the electrodes are indicated by green arrows. Top and bottom views are shown. Scale bars are not provided as this chamber is currently in the process of being patented.

ERG Final Setup

After the dissection and chamber mounting, the final setup for the ERG rig was performed before the experiments started. The 300 mL bottle of Locke's solution was placed into the gravity fed perfusion system, the ERG dual retinae chamber was connected to the perfusion system in the ERG rig, the 95% O_2 and 5% CO_2 were bubbled in the Locke's solution, and the electrodes from the chamber were connected to the ERG headstage detect. The electrodes were placed above and below the retinae in order to measure the voltage difference across the retinae when a light, or a stimulus, was flashed onto the retinae (Figure 5). The perfusion flowed down from the top of the ERG rig to the chamber and emptied into a beaker under the ERG rig. The solution was perfused for ten minutes before the experiment began. When experiments were running, the faraday cage was lowered in order to minimize the noise in the recordings.

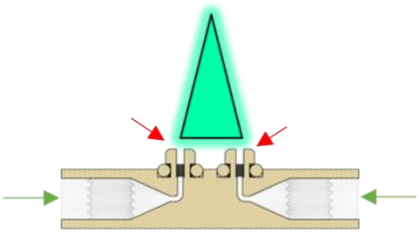

Figure 5. Example schematic of the light stimulus flashing onto the ERG chamber, where the retinae would be placed. The retinae would be placed at the red arrows and the electrodes are indicated by green arrows. The green light is the color of the light flashed at 490 nm.

Ex-vivo ERG Experimental Recording Conditions

The recording conditions were kept as close as possible to the natural environment of the zebrafish retinae. Locke's solution was continuously perfused throughout the chamber in order to keep the tissues viable. The temperature of Locke's solution was originally set at 37°C within the

ERG rig, however it was later changed as it was discovered that zebrafish tissues were more delicate than mice tissues, so the high temperature was killing cells in the retinae and negatively impacting the responses. The inline heater was turned off and the temperature was changed to room temperature, which was approximately 22°C.

ERG Experimental Procedure

Photoreceptors were stimulated at a wavelength of 490 nm originally, which was the optimal wavelength used for rod responses in mice, but was later changed to 505 nm, as that wavelength produced more optimal responses in zebrafish retinae. The intensity of light stimulus varied from scotopic intensities to photopic intensities. In order to isolate the A and B wave of the electrical response, chemical blockers were added into Locke's solution. A schematic representation of the locations of the A and B waves in an ERG response with no chemical blockers is shown in Figure 6. To isolate the B wave, 0.15 g of BaCl were added into the 300 mL Locke's solution. To isolate the A wave, 0.15 g BaCl and 500 µL of L-2-amino-4-phosphonobutyric acid (L-AP4) were added into 150 mL Locke's solution. Those solutions perfused through the ERG rig and when it was time to isolate the specific waves, replaced the 300 mL Locke's solution in the gravity fed perfusion system. In each of the perfusions, five rounds of differing light stimulus were applied per each solution change. The LED light was set to the 1% intensity and four different ND filters were used to filter and reduce the light stimulus. The intensity with no light filters was also used for a total of five different light intensity recordings per solution.

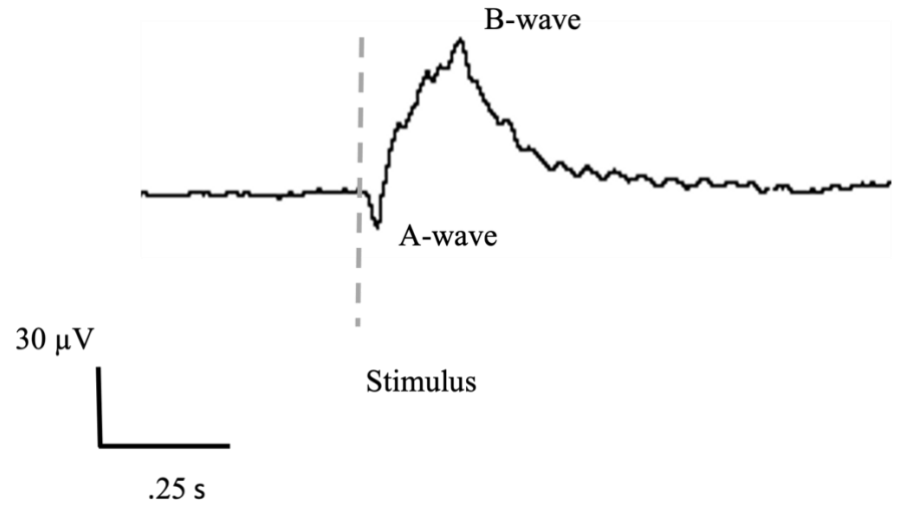

Figure 6. Example of an ERG response with the A-wave and B-wave labeled. The dotted line represents the stimulus.

Computer Analysis

Excel was used for data calculations and statistical analysis. Clampfit was used to graph the ERG responses. The recordings were filtered in order to remove any noise present in the recordings.

Results

It was found that an *ex-vivo* ERG can be conducted on zebrafish retinae and a light response can be obtained. At differing light intensities, measured in log photons, zebrafish photoreceptors had varying maximal responses (Figure 7). These experiments were run with just Locke's solution and no isolation of the A or B wave was performed. The light intensity was measured through log photons which were found by using the ND filter strength, the intensity of the light stimulus, and the length of time the stimulus is flashed in order to determine the number of photons present in the light stimulus. The green dashed line represents the time at which the

light stimulus was flashed, and the color of the dashed line corresponds to the color of 490 nm light stimulus. As shown in Figure 7, the photoreceptors had the same maximal response for log photons 2.58 and 3.18, indicating that the photoreceptors were saturated. Due to scotopic intensities being around 1 log photons/μm^2, mesopic intensities being around 2 log photons/μm^2, and photopic intensities being around 3 log photons/μm^2, it was shown that zebrafish photoreceptors saturate at between scotopic and mesopic intensities, near 2 log photons/μm^2. These responses were obtained at 37°C. The maximal response recorded was approximately 30 µV.

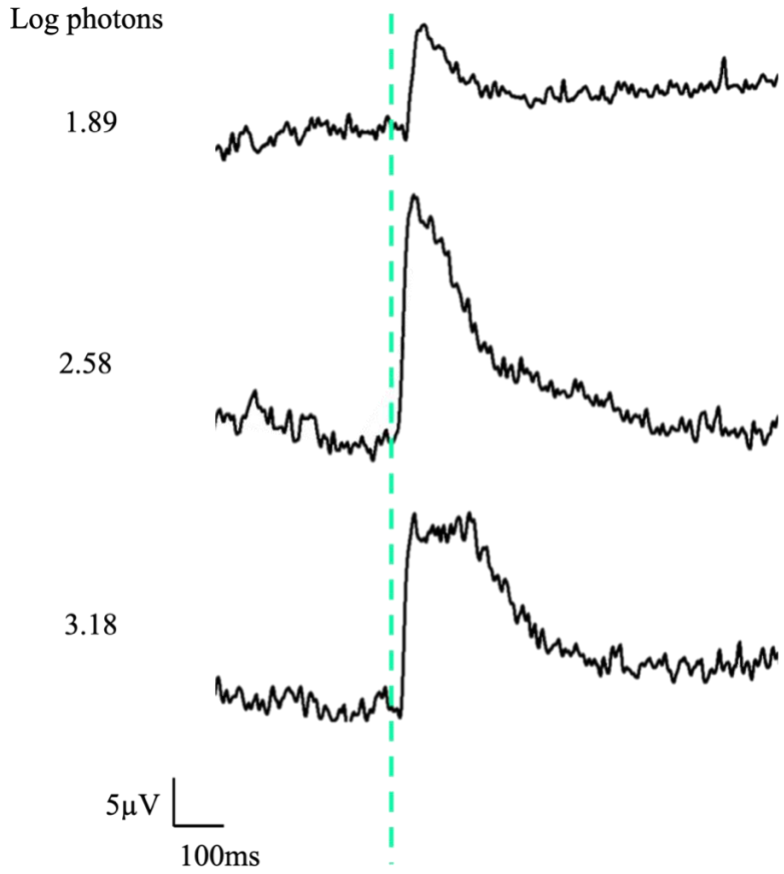

Figure 7. Representative photoreceptor light responses of zebrafish retina at 490 nm with Locke's solution. The light stimulus is represented by the green dashed line. Light intensity measured in log photons is shown to the left of the curve.

Next, identical experiments were performed, but with two differences in the ERG recording conditions: the temperature and the wavelength of light. In these experiments the temperature of inline heater was changed in order to determine if temperature was affecting the size of the zebrafish ERG responses, as mice ERG responses were observed to be larger based on experiments run by a graduate student. The temperature was kept at room temperature, approximately 22°C, instead of 37°C. The wavelength of light stimulus was also changed from 490 nm to 505 nm in order to better capture the responses of the photoreceptors, as the increased wavelength was thought to elicit larger responses. As shown in Figure 8, the responses of zebrafish retinae to the same intensity and amount of light stimulus were much greater, with a maximal response of 84 μV, a 94.7% increase in response from Figure 7 values obtained at the higher temperature and lower wavelength of stimulus. The green dashed line in Figure 8 shows the moment at which the light stimulus was flashed, and the color of the dashed line corresponds to the color of 505 nm light.

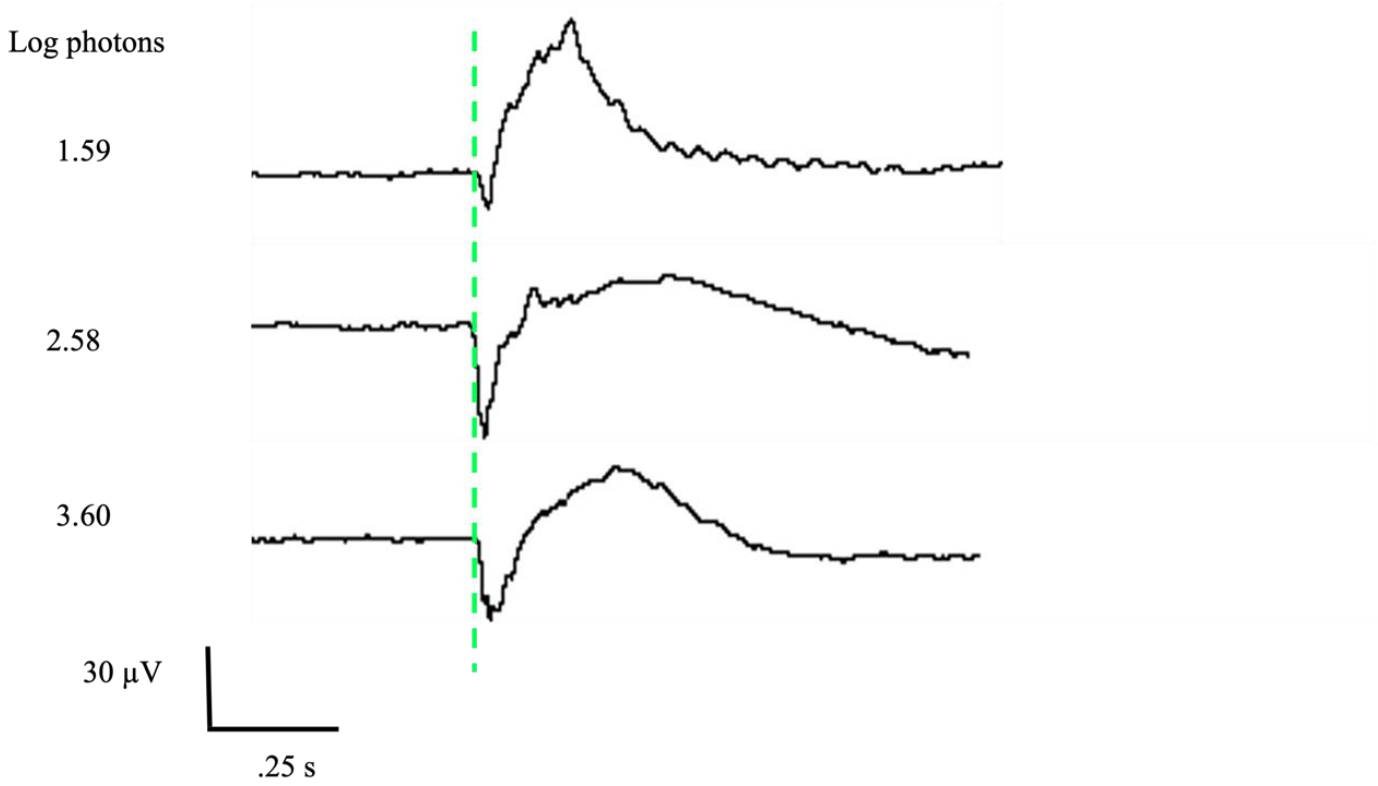

Figure 8. Representative photoreceptor light responses of zebrafish retina at 505 nm with Locke's solution. The light stimulus is represented by the green dashed line. Light intensity measured in log photons is shown to the left of the curve.

After the ideal temperature and wavelength were found that caused the maximal response of zebrafish retinae based upon the mouse protocol and trial-and-error within experiments, isolation of the A and B waves was pursued. Chemical blockers were used to isolate specific components of the retinal responses in zebrafish retinae. First, the isolation of the B wave was performed by replacing the Locke's solution in the gravity-fed perfusion chamber with 30 0mL of Locke's solution supplemented with 0.15 g of BaCl. From this solution, the B wave of the ERG response was able to be extrapolated, as shown in Figure 9. In these experiments the modified protocol of room temperature and 505 nm were used. The maximal response of the B wave was found to be 207 µV. The maximal response is not shown in the representative traces

below but was the largest response in the data set collected, as the below traces are the cleanest representatives of the recordings collected. The A wave is still present in these recordings as the B wave does not occur without the A wave, so both are present in primary recordings, however through data analysis with the isolation of the A wave responses, the isolated response of the B wave in µV can be found.

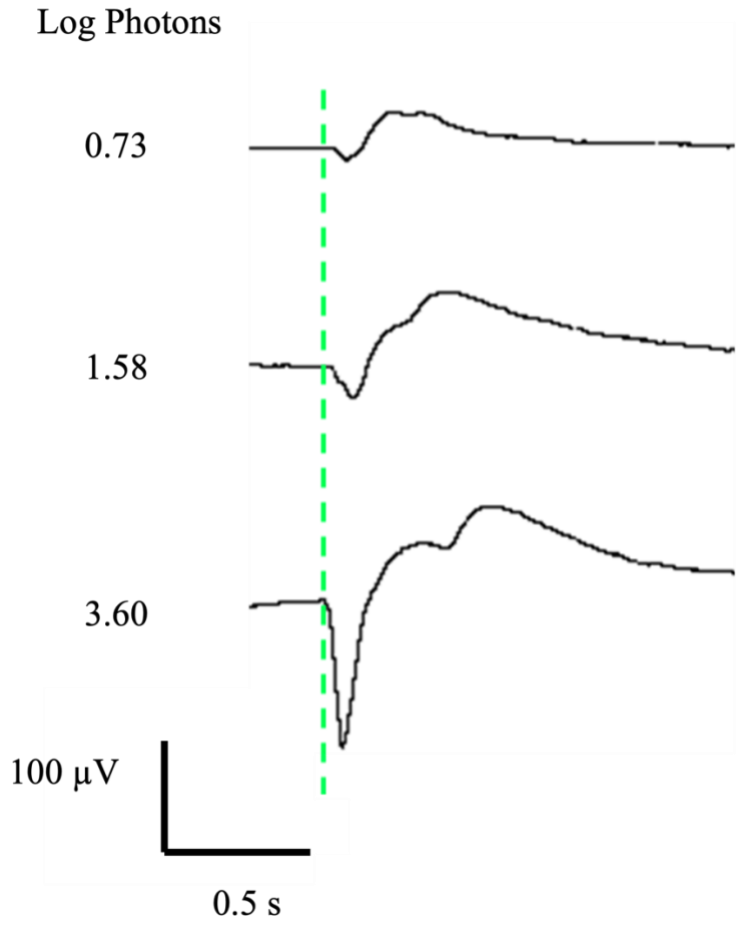

Figure 9. Representative photoreceptor light responses of the isolated B wave of zebrafish retina at 505 nm with BaCl and Locke's solution. The light stimulus is represented by the green dashed line. Light intensity measured in log photons is shown to the left of the curve.

An intensity response (IR) curve was also created from the ERG responses in order to determine the half-maximal response of the isolated B wave, which shows the intensity that

induces a response halfway between the maximum and minimum responsivity (Figure 10). The IR curve was created by plotting the responsivity of the retinae against the log photons/μm^2 that were used as the stimulus. As shown in Figure 10, the half-maximal response was 1.35 log photons/μm^2, indicating that saturation occurs at scotopic intensities for the B wave isolation of the zebrafish retinal response.

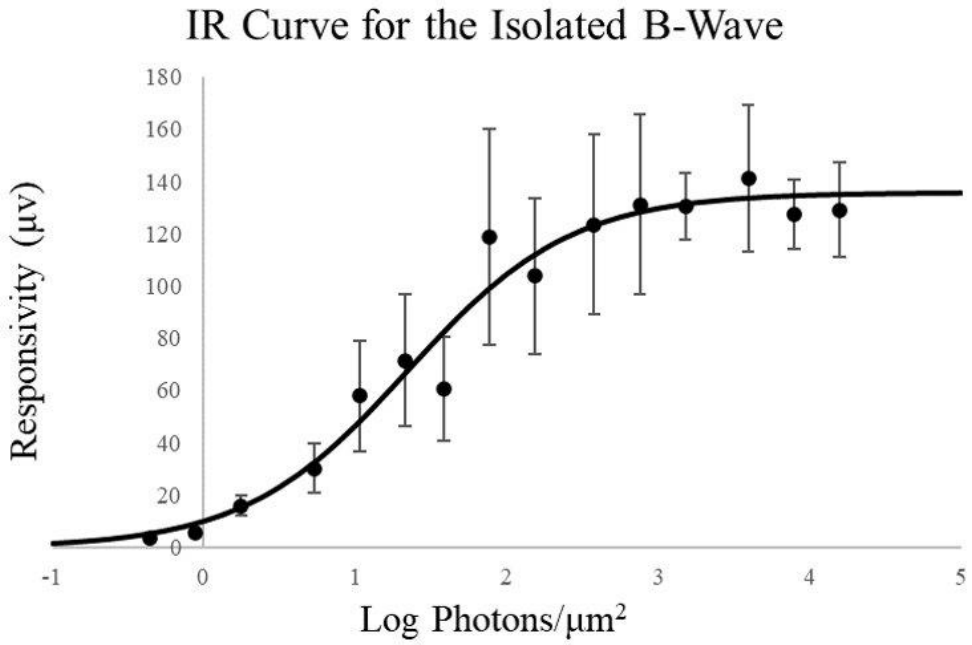

Figure 10. Intensity response curve of the maximum B-wave responses at varying light intensities. The half maximal response value was 1.35 log photons/μm^2. Error bars represent SEM (n=3).

Next, the isolation of the A wave occurred and was performed by replacing the Locke's solution in the gravity-fed perfusion chamber with 150 mL of Locke's solution, 0.15 g of BaCl, and 500 μL of L-AP4. From this solution, the A wave of the ERG response was extrapolated, as shown in Figure 11. In these experiments the modified protocol of room temperature and 505 nm were used. The maximal response of the A wave was found to be 40 μV.

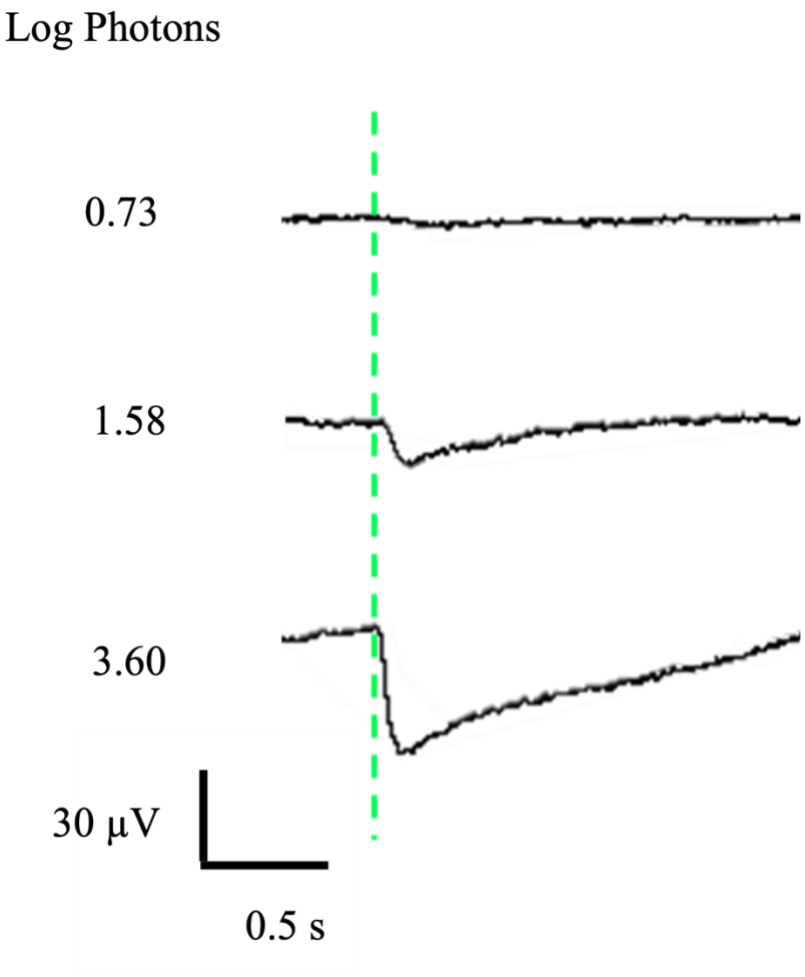

Figure 11. Representative photoreceptor light responses of the isolated A wave of zebrafish retina at 505 nm with BaCl, L-AP4, and Locke's solution. The light stimulus is represented by the green dashed line. Light intensity measured in log photons is shown to the left of the curve.

An IR curve was also created from the ERG responses in order to determine the half-maximal response of the isolated A wave (Figure 12). The IR curve was created by plotting the responsivity of the retinae against the log photons/μm^2 that were used as the stimulus. As shown in Figure 12, the half-maximal response was 1.64 log photons/μm^2, indicating that saturation occurs at scotopic intensities for the A wave isolation of the zebrafish retinal response. The time

to peak of the isolated A-wave responses were also determined in order to find the time needed for the A wave to reach maximum amplitude, or its peak, as shown in Figure 13.

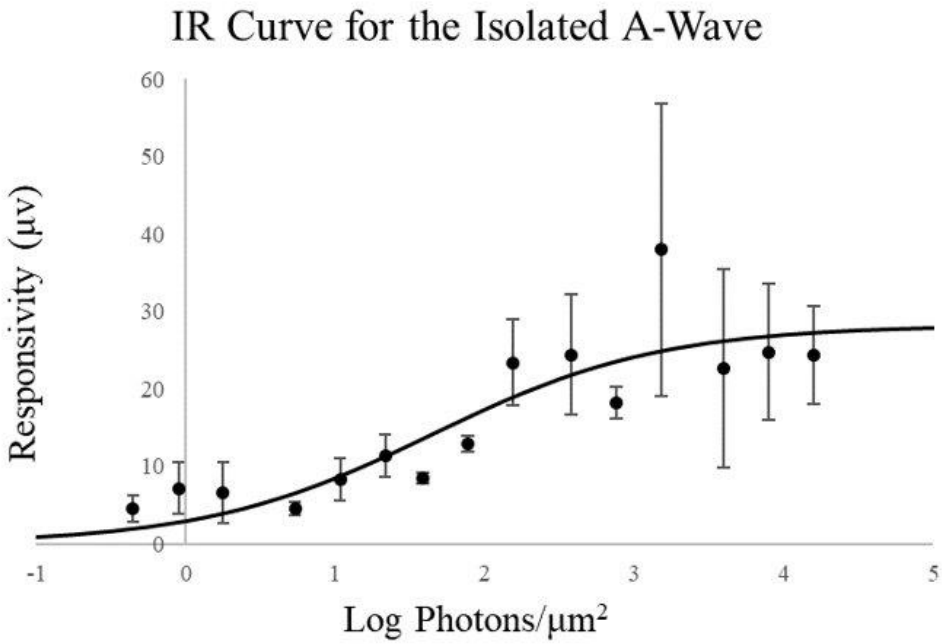

Figure 12. Intensity response curve of the maximum A-wave responses at varying light intensities. The half maximal response value was 1.64 log photons/μm^2. Error bars represent SEM (n=3).

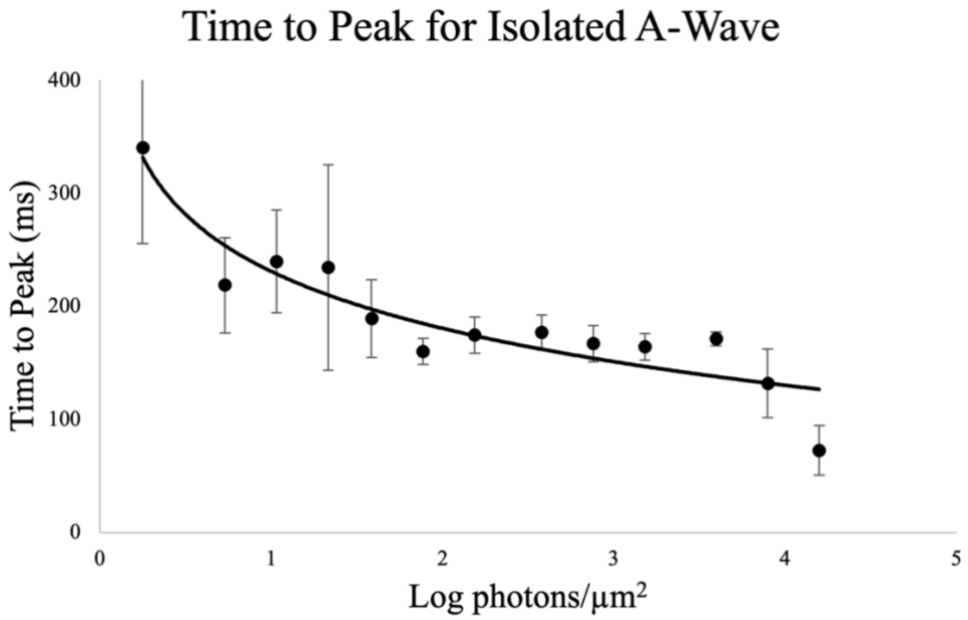

Figure 13. Time to peak of the isolated A-wave response at varying light intensities. Error bars represent SEM (n=3).

Discussion

From the ERGs conducted on zebrafish retinae, it was found that differences in protocol from mouse to zebrafish retinae can be identified and modified for ideal ERG responses from zebrafish. First, the differences in the protocol for the mouse and zebrafish retinae were the temperature the ERG was run at, the wavelength of light stimulus, and the dissection techniques. Figures 7 and 8 show the difference in the maximal response that temperature and wavelength of the light stimulus cause. Figure 7's recording conditions had the higher temperature at 37°C and a wavelength of 490 nm, while Figure 8's recording conditions had a temperature of approximately 22°C, which was the room temperature, and a wavelength of 505 nm. Figure 7's recording traces had a smaller maximal response, with the largest response being 30 µV compared to Figure 8's recording traces having the largest response being 84 µV, a 94.7%

increase in maximal response. The difference in temperature was thought to be due to the zebrafish's ideal temperature being 26-28.3°C, indicating that the original temperature was too hot to mimic the retina's natural environment, impacting the ERG responses (Advesh et al., 2012). The alteration of the temperature the ERG was run at and the wavelength of the light stimulus from the mouse ERG protocol elicited larger responses. Secondly, the dissection techniques used for the zebrafish retinae were slightly different from the mouse retinae. The dissection required much more precision and smaller tools than the mouse dissections and a protocol was streamlined for the zebrafish dissection that was outlined in the methods and materials section that has continued to be used.

It was also found that an *ex-vivo* ERG can be conducted on zebrafish retinae, a light response can be obtained, and the A and B waves can be isolated. Figure 8 shows the ERG response to differing intensities of light in Locke's solution with no chemical blockers present. The ERG responses show that obtaining an *ex-vivo* ERG on zebrafish retinae is possible, which leads into the many possible experiments and data collection that can be done with zebrafish ERGs. One possible experiment that was done was the isolation of B and A waves through chemical blockers, as shown in Figures 9 and 11, respectively. The isolation of A and B waves is important due to their physiological significance, as discussed in the introduction. The IR curves of the ERG responses were used in order to determine the light intensity that zebrafish photoreceptors saturate, as shown in Figures 10 and 12, and demonstrated that zebrafish retinae responses fit a nonlinear intensity response function. The half-maximal response of the isolation of the B waves was 1.35 log photons/μm^2, indicating that saturation occurs at scotopic intensities and was 1.64 log photons/μm^2 for the isolation of the A waves, indicating that saturation occurs at scotopic intensities. From these responses, it was determined that zebrafish photoreceptors

saturate at dim light intensities in the scotopic light intensity range and have a high sensitivity to light.

Through determining if a light response can be obtained, future study of the zebrafish visual system can be conducted as zebrafish can be used to study different genetic zebrafish lines and zebrafish specific photoreceptor responses, such as rods and cones. There are many diseases that affect the physiology of the retinae and the visual system, such as retinoblastoma and retinoschisis, and many others that do not mainly affect the visual system but in which the visual system could be useful for early detection, such as Alzheimer's disease. Zebrafish are an ideal model organism for the advancement and continued studies of classification, treatment, and diagnosis of widespread human diseases. The finding that ERGs can be performed on zebrafish retinae and elicit defined light responses is only a first step into the importance that photoreceptor and visual physiology of a zebrafish has in the field of electrophysiology and medicine.

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Zebrafish electroretinogram responses

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Honors Research Project

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