The Role of Alpha Melanocyte Stimulating Hormone (α-MSH) in Ocular Disease

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Dr. Sharon Fekrat

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Research Summary

Purpose of the Study:

We aim to study the ocular levels of alpha melanocyte stimulating hormone in the aqueous humor of patients with severe geographic atrophy. As there currently are no therapeutic options for these patients, further research into potential therapeutic targets such as α-MSH, is of utmost importance.

Background & Significance:

Macular degeneration is a disease of the retina affecting the elderly. There are two forms of macular degeneration: dry and wet macular degeneration. Wet macular degeneration may be treated with anti-vascular endothelial growth factor (anti-VEGF) injections. Dry macular degeneration is slowly progressive and in its most advanced form causes severe atrophy and vision loss. There is currently no treatment for dry macular degeneration.

The melanocortin system encompasses multiple peptides including α-, β-, γ-melanocyte stimulating hormone (MSH) and adrenocorticotropic hormone (ACTH). There are five MC receptors (MCR1-5) that are expressed in a multitude of cells and tissues. Alpha melanocyte stimulating hormone is widely expressed in the tissues such as the hypothalamus, skin and retina. [1]

There are several known effects of α-MSH including suppressing pro-inflammatory signals, promoting production of anti-inflammatory cytokines, inducing suppressor antigen presenting cells, inducing activation of regulatory T cells, and regulating the immunity in healthy eyes. [2–5]

Retina pigment epitheial (RPE) cells have been shown to be a source of α-MSH. RPE cells in culture produce 2 ng of α-MSH in 24 hours. There is possible loss of α-MSH in eyes with autoimmune disease or damaged retinas. Alpha MSH may increase RPE and photoreceptor cell survival. Both RPE and photoreceptors express melanocortin receptors through which alpha MSH promotes cell survival.[6] In an experimental rat model for example when α-MSH analog was injected into the eyes of rats with retinal dystrophy photoreceptor rescue was seen through to the hormone's neurotrophic activity.[7] Additionally another study showed α-MSH protected RPE cells against oxidative stress.[8]

Alpha-MSH is a molecule that is extremely probe to proteolysis, even when removed from animal or human eyes it is prone be being quickly denatured. This is why human eyes of living subjects are the best sample for the most accurate analysis of α-MSH

levels. Levels in normal eyes undergoing cataract surgery have been previously measured in one study of 8 eyes. The mean level in these eyes was 20pM with a range of 8-31 pM.[9] As the concentration of α-MSH in the aqueous of normal eyes has previously been published, the next step is to describe levels in eyes with pathology, such as advanced macular degeneration.

Alpha MSH is a hormone that has been shown to be found in the eye. The goal of this study is to see if levels of this hormone are affected by advanced dry macular degeneration. As macular degeneration is a clinical diagnosis based on exam and imaging findings, levels of alpha mSH should not and will not be considered a diagnostic test for this disease.

Currently there are no treatment options for patients with severe geographic atrophy. This is a blinding disease without a therapeutic option. Learning more about the levels of alpha MSH in patients with geographic atrophy may be beneficial in further understanding the disease and potential treatment options.

We hypothesize that eyes with advanced geographic atrophy will have decreased levels of alpha MSH as compared to normal controls. As there are potential ways to supplement α-MSH in the eye and bloodstream, the finding of a low level of alpha MSH would be significant as it may provide a new potential therapeutic pathway to explore. The control used will include the prior published study of levels in 8 human eyes and the normative controls that will be gathered during routine cataract surgery during this study.

Design & Procedures:

If the subject decides to participate, the informed consent process will be completed. After completing the consent form, subjects will be asked to complete a short memory test, the Montreal Cognitive Assessment (MoCA), blind version (attached to IRB submission), to be administered by one of the key personnel. An aqueous paracentesis will be then be performed as follows:
The anterior chamber paracentesis will be performed using povidone iodine preparation and post-procedural topical antibiotics. After informed consent is obtained the eye will be anesthetized using topical anesthesia. The lids will be cleaned with 10% povidone iodine and one drop of 5% povidone iodine will be applied to the ocular surface. A lid speculum will be placed to retract the eyelids. A 27-gauge needle will be placed through the clear cornea to aspirate approximately 100 µl of aqueous humor. Following the procedure, prophylactic topical antibiotics will be given for 3 days.

The patient will be re-examined for possible immediate complication such as bleeding, hypotony or corneal scratch 20 minutes after the procedure at the slit lamp.

In 10 eyes of patients recruited prior to routine cataract surgery a careful anterior chamber paracentesis will be performed through the clear cornea immediately after the sideport incision is made. Care will be taken to avoid inadvertent introduction of blood into the syringe.

Once collected the samples will be frozen at -80 degrees Celsius. The samples will then be sent by secure shipment to an outside lab to measure levels of α-MSH in aqueous samples using ELISA. Specifically, the samples will be sent to Dr. Andrew Taylor at Boston University who is a world expert in the measurement of alpha MSH in the eye using ELISA assays. Dr. Taylor has IRB approval for the measurement of alpha MSH in ELISA assays at Boston University under approval number H-32859 with original approval date 4/14/14. All of the samples sent to Dr. Taylor's lab will be de-identified so he has no patient health information.

A follow-up phone call will be made 5 days after the procedure for subjects with geographic atrophy to assure the eye feels back to baseline and the patient does not need closer follow-up. Control subjects will be asked to follow with their cataract surgeon for normal post operative checks as per the cataract surgeon (usually day 1, week 1 and month 1 after surgery).

Selection of Subjects:

The subject population will consist of up to 50 volunteers from the Duke Eye Center's vitreoretinal clinic. All subjects will be 60 years of age or older. Subjects with severely limited vision or blindness from geographic atrophy and only those patients who are pseudophakic or aphakic will be included in the study. Subjects must have a best corrected visual acuity of 20/100 or worse in the eye undergoing the procedure. If subjects with advanced macular degeneration are undergoing cataract surgery then the sample of aqueous will be obtained at the time of cataract surgery. Very few patients with geographic atrophy undergo cataract surgery. Enrollment solely from cataract surgery patients would be too low for results from the study to be meaningful. This is due primarily to the fact that in many patients with advanced geographic atrophy in the setting of macular degeneration, cataract surgery has most likely been previously performed due to their age. Second, if cataract surgery has not been performed it is often not recommend as it is unlikely to further improve their vision given the degree of vision loss from geographic atrophy. We propose to include eyes with only severe geographic atrophy with best corrected visual acuity of 20/100 or worse.

Additionally, we will also attempt to get normative data on α-MSH levels to compare to previously reported levels and aim to gather 10 samples in healthy eyes at the time of cataract surgery. Every reasonable attempt will be made to include subjects from all races.

Subject Recruitment & Compensation:

Subjects with geographic atrophy and control subjects will be recruited by Dr. Sharon Fekrat or Dr. Dilraj Grewal from their vitreoretinal clinics during standard-of-care visits at the Duke Eye Center. Controls will also be recruited form Dr. Terry Kim's patients that are having cataract surgery.

Subjects will not be compensated for their participation in this study.

Consent Process – see Section 14 of the e-IRB submission form and complete the questions in that section.

Dr. Sharon Fekrat (Principal Investigator) or other IRB listed staff for this project will conduct the consent process prior to enrolling subjects. Each portion of the consent will be reviewed with the subject with ample time provided to the subject for discussions/questions prior to enrolling onto the study. A copy of the consent will be given to the subject if they choose to participate.
Patients with poor vision will have the consent form read to them in the presence of an impartial witness.

Subject's Capacity to Give Legally Effective Consent:

Only subjects able to understand the informed consent process and with legal capacity to give consent will be included in the study.

Study Interventions:

There will be no study interventions apart from those described in #4 above.

Risk/Benefit Assessment:

While these patients will have significantly limited vision due to exceedingly advanced macular degeneration, the study poses certain risks to the patient. There is a low but serious risk of inoculation of the eye with an infectious organism. The risk of endophthalmitis from aqueous paracentesis has not been published or studied, however is much lower than that of a vitreous tap or intravitreal injection, which has a low rate of endophthalmitis of 0.05% or less. The previously published studies of patients undergoing AC paracentesis for uveitis have reported a 0% rate of serious infection such as endophthalmitis.[10,11]

Other risks to consider include bleeding due to pressure change or inadvertent damage to the ocular structures by the needle and leaking from the needle track. A corneal

scratch may also occur during this procedure. Precautions, such as cleaning of the eye prior to the procedure and antibiotic use after the procedure, will be taken to minimize these risks.

We will additionally examine the anterior chamber 20 minutes post-procedure as most complications such as hyphema (bleeding in the eye), leak from the needle track, or corneal scratch would be apparent during this time frame.

As the eyes that will be chosen for the study will be pseudophakic there will be no risk of cataract or trauma to the lens which is the most worried about complication of an aqueous tap.

While study subjects will not receive immediate direct benefit, the data acquired may provide valuable information that will support the potential understanding and possible development of therapeutics in disease without current therapeutic options.

Potential loss of confidentiality is a risk of any study however we will take every precaution to keep patient health information confidential.

Costs to the Subject:

There will be no financial costs to the subjects for study participation. However, the subject would remain responsible for the costs of their clinical care, which are independent of this study.

Data Analysis & Statistical Considerations:

At this stage, only quantitative analysis of alpha MSH levels will be performed.

Data & Safety Monitoring:

We do not anticipate that the risk for adverse events will be any higher than for other commonly performed aqueous paracentesis in the clinic setting. Specifically, we do not anticipate any adverse event as a result of study participation in the study as every precaution will be taken to decrease the risk of potential infection. Additionally, by including only patients who have had prior cataract surgery (pseudophakic) or no lens (aphakic), there is no risk for trauma to the lens or induction of a cataract. The PI's contact information will be available to each enrolled subject should a late event occur. The investigator will review and sign off on all adverse events and problems as they occur and they will be reported to the IRB per Duke IRB policies.

Privacy, Data Storage & Confidentiality – see Section 12 of the e-IRB submission form and complete the questions in that section.

Collected clinical data, including a single master list to relink the study ID to the subject, will be stored on password-protected, hard drive encrypted departmental computers in the Department of Ophthalmology. Data will be stored in the P:drive in a secured folder under the PIs name. Only the study staff will have access to these files.

References:

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