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ISER 2024
PROGRAM ABSTRACTS

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dark-adapted human observers in conditions where single photons are being captured among thousands of photoreceptors, characterizing their ability to summate sparse photon captures spread over time or across the surface of the retina. For this purpose, we leverage human psychophysics and the pupillary light response (PLR) as proxies for the conscious and non-conscious visual systems. Through a two-alternative forced-choice task, participants were tested in their ability to consciously detect light stimuli varying in intensity, timing, and spatial extents. Simultaneously, videos of their pupils were recorded, and the PLR threshold was determined by subjecting the obtained PLR traces to a two-interval forced-choice ideal observer analysis.

We report three primary findings: 1) When light is distributed across the whole visual field, the PLR matches the threshold sensitivity of the conscious visual system, responding to the capture of individual photons across tens of thousands of rod photoreceptors. 2) The integration time of the PLR is indistinguishable from that of conscious vision. 3) As light stimuli are made progressively smaller at the surface of the retina, the PLR becomes progressively less sensitive as compared to the conscious visual system.

Our experiments support that the most sensitive retinal pathway – the rod bipolar pathway – drives both the pupil and conscious vision at the limit of visual sensitivity. Considering the differences in the dendritic morphology between ipRGCs and the most sensitive RGC types driving image forming vison, we put forward an explanation for how the pupil behaves as an illumination sensor that is by enlarge insensitive to spatial scales, while the image forming vision is highly sensitive to spatial scales. The PLR constitutes a powerful window to study the processing of signals arising from the outer retina in dim light in human subjects non-invasively.

RPE-Choroid

Abstract ID: 270

Pharmacological inhibition of the Phospholipase D (PLD) pathway prevents oxidative stress in retinal pigment epithelium cells exposed to high glucose levels

Poster number: T-58

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Introduction
Together with inflammation, oxidative stress (OS) is involved in the pathogenesis of several retinal diseases. Canonical phospholipases D (PLD1 and PLD2) hydrolyze phosphatidylcholine (PC) to release choline and phosphatidic acid (PA), which can be dephosphorylated by lipid phosphate phosphatases (LPPs) to diacylglycerol (DAG). We previously demonstrated that PLD1 and 2 mediate the inflammatory response of retinal pigment epithelium (RPE) cells induced by high glucose (HG) levels. Furthermore, a significant increase in reactive oxygen species (ROS) was observed in RPE cells exposed to HG.

Objectives
This study explores the modulation of OS mediated by PLD inhibition in RPE cells exposed to HG.

Methods
RPE cells (ARPE-19 and D407) were exposed to HG (33 mM) or control conditions (NG, 5.5 mM). In order to mimic PLD/LPPs activation induced by HG, cells were treated with 100 µM dilauroyl PA (DLPA), 100 µM dioctanoyl glycerol (DOG) or with 50 µM DLPA + 50 µM DOG. PLD1, PLD2, cyclooxygenase-2 (COX-2) and NADPH oxidases (NOX), were inhibited using VU0359595 (PLD1i, 0.5 µM), VU0285655-1 (PLD2i, 0.5 µM), celecoxib (10 µM) or DPI (5 µM), respectively. Immunocytochemistry, fluorescent proves and western blots assays were performed to evaluate reactive oxygen species (ROS), mitochondrial membrane potential (MMP), glutathione (GSH) levels and Nrf-2 pathway.

Results
HG-exposure significantly increased ROS levels and reduced MMP in both RPE lines, with respect to NG. PLD inhibitors prevented both effects in an Nrf2 and COX-2-independent manner. Also, exogenously added DLPA and DOG increased OS and reduced MMP. The NOX inhibitor DPI was able to prevent OS induced in RPE cells exposed to HG and also in cells exposed to DLPA+ DOG.

Conclusion
Our previous findings together with results presented herein, demonstrate that PLD1 and 2 inhibition not only prevents the inflammatory response of RPE cells, but also decreases OS generated in RPE cells exposed to HG, possibly through a reduced NOX activity but in an Nrf-2 and COX-2 independent manner. The PLD/LPP pathway constitutes a novel pharmacological target to prevent, at the same time, OS and the inflammatory response, two hallmarks of several retinal diseases.

Abstract ID: 283

PNPLA3 role as a negative regulator of retinyl ester hydrolase activity and the visual cycle

Poster number: T-59

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PNPLA3 Role as a Negative Regulator of Retinyl Ester Hydrolase Activity and the Visual Cycle

Introduction
Retinyl esters are stored in retinosomes in the RPE and serve as the substrate for RPE65 to generate 11-*cis*-retinol. However, RPE65 localizes in ER and is not associated with retinosomes; therefore, it was unclear how RPE65 accesses retinyl esters in retinosomes. Recently, we have demonstrated that Patatin-like phospholipase domain-containing protein 2 (PNPLA2) mobilizes retinyl esters from retinosomes and stimulates the production of 11-*cis*-retinol by RPE65. Patatin-like phospholipase domain-containing protein 3 (PNPLA3) is highly expressed in the retina and showed retinyl ester hydrolyzing activity in vitro. However, the role of PNPLA3 in the visual cycle and its function as retinyl ester hydrolase (REH) in vivo is uncertain.

Objectives
The present study aimed to determine the contribution of PNPLA3 in retinoid metabolism in the RPE and its potential role in the visual cycle.

Methods
We have analyzed the visual function and its recovery after complete photo bleach in PNPLA3 ko mice using electroretinography (ERG). Retinoid profile recovery after dark adaptation was measured by HPLC. HEK 293 cells were incubated with 20 μM retinol for 24 h and adenoviral vectors expressing PNPLA3, PNPLA2, and CGI-58 (co-activator of PNPLA2). REH activity was quantified by the remaining intracellular retinyl ester level or with a liposome assay. RPE65 activity was measured by the generated 11-*cis*-retinol and analyzed by HPLC.

Results
Kinetics of 11-*cis*-retinal regeneration in the dark following light exposure were significantly faster in PNPLA3 ko mice compared with age-matched WT mice. Furthermore, PNPLA3 ko mice showed higher ERG a-wave recovery than WT mice, suggesting faster dark adaptation, although it did not reach statistical significance. Cell culture studies showed that, in contrast to PNPLA2, PNPLA3 increased retinyl ester level compared to control. Moreover, PNPLA2 has a significantly higher REH activity than PNPLA3 under the same condition. CGI58 significantly increased the REH activity of PNPLA2. At the same expression level, CGI58 did not change the REH activity of PNPLA3. Interestingly, retinol isomerase activity of RPE65 decreased when it was co-expressed with PNPLA3 in 293-LRAT cells.

Conclusion
These results suggest that PNPLA3 may be a negative regulator of REH activity in the RPE and the visual cycle.