A647

ACID-SENSING ION CHANNELS 2 AND 4 (ASIC2, ASIC4) ARE REGULATED BY LIGHT IN THE ZEBRAFISH RETINA

ARVO 2012

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PURPOSE

Acid-sensing ion channels (**ASICs**) are H^+-gated cation channels that monitor deviations from the physiological values of extracellular pH. ***ASIC*** genes in zebrafish (**zASICs**) are expressed in the central nervous system and the retina. pH variations in the retina are thought to be involved in the fine-tuning of visual perception and in the adaptation of the retinal responses to different light intensities. Moreover, ***ASIC2*** knock-out mice are also more sensitive to light-induced retinal degeneration.

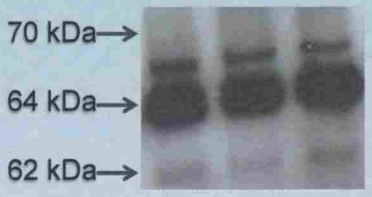
This study examines the effects of continuous light or darkness exposure in the mRNA levels and cell distribution of **ASIC2** and **ASIC4** in the retina of adult zebrafish.

METHODS

The retinas of adult zebrafish exposed to light-darkness rhythm, or to continuous light (10 days) or continuous darkness (10 days) were studied. Total RNA was extracted from retinas isolated from adult zebrafish. Levels of mRNA for the genes **zASIC2**, and **zASIC4** were determined by qRT-PCR, and the cell localization using immunohistochemistry.

RESULTS

Detectable **ASIC2**, **ASIC2** and ASIC4a mRNA levels were detected in the adult zebrafish retina. The protein products of both **ASIC2** isoforms were detected in the photoreceptor cells, pleximorm layers and ganglion cells layers and the optic fascicle; **ASIC4** immunoreactivity was detected in the photoreceptor cells and ganglion cell layer. Continuous light exposure resulted in decrease levels of **ASIC2** mRNs and the proteins were detected in the same cells as in control; **ASIC4** mRNA levels were up-regulates and the intensity of immunainig as well. Continuous darkness exposure resulted in not changes neither in **ASIC4** mRNA levels or protein expression, whereas down-regulates **ASIC2** mRNAs and the immunoreactivity was absent.



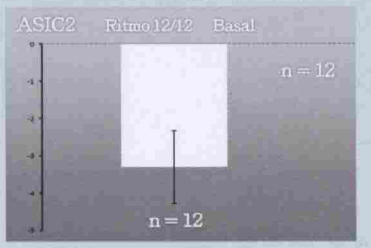
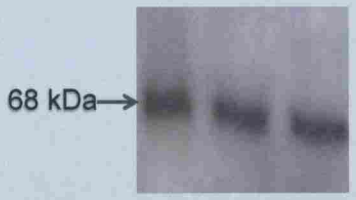


Fig. 1.- Wstern-blot ASIC2



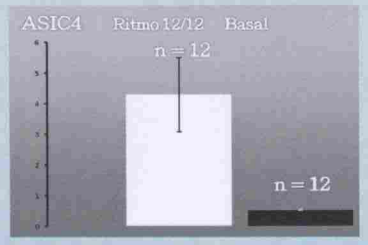


Fig. 3.- Wstern-blot ASIC4

ASIC 2

Light rythm	12/12 (Basal)
Continuous light exposure	**-3,311 ± 0,98** (n = 12)
Continuous darkness exposure	**Non detectable** (n = 12)

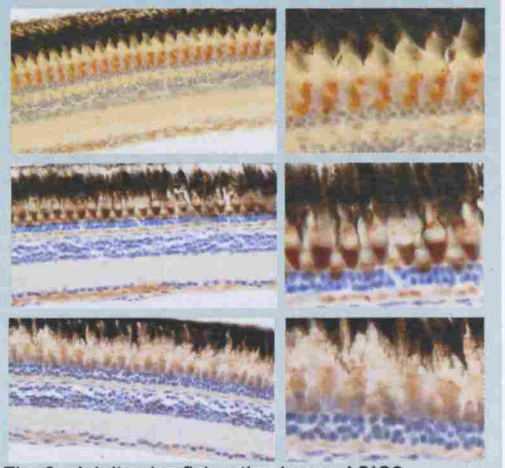


Fig. 2.- Adult zabrafish retina image ASIC2

ASIC4

Light rythm	12/12 (Basal)
Continuous light exposure	**4,29 ± 1,21** (n = 12)
Continuous darkness exposure	**0,52 ± 0,02** (n = 12)

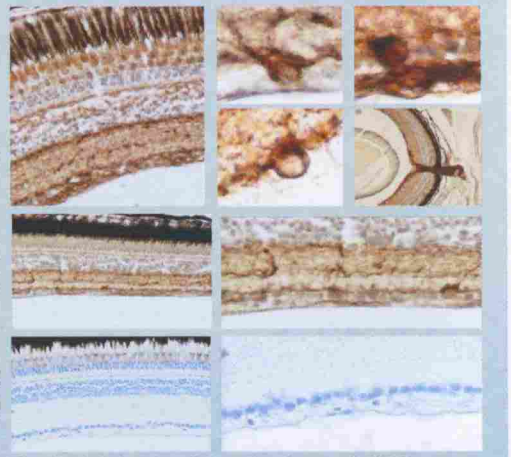


Fig. 2.- Adult zabrafish retina image ASIC2

CONCLUSIONS

The variations in the expression of **ASIC2** and **ASIC4** genes and proteins after continuous light and darkness exposure demonstrate that they are regulated by light and suggest changes in the extracellular pH that must be regulated in these environmental conditions.

PROGRAM SUMMARY

ARVO 2012

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768 — *A645* **Modulation of Glutamate Release by Endogenous Zinc at Photoreceptor Terminals.** *Ivan Anastassov[1,2], R. Chappell[1,2].* [1]Biology, Hunter College & Graduate Center CUNY, New York, NY; [2]Cellular Dynamics Program, Marine Biological Laboratory, Woods Hole, MA.

769 — *A646* **Immunocytochemical Localization Of The Voltage-gated Calcium Channel α2δ4 Subunit In The Rodent Retina.** *Luis Perez de Sevilla Muller, J. Liu, A. Solomon, A. Rodriguez, N. Brecha.* Department of Neurobiology, UCLA University, Los Angeles, CA.

770 — *A647* **Acid-Sensing Ion Channels 2 And 4 (Asic2 Asic4) Are Regulated By Light In The Zebrafish Retina.** *Celia Sanchez-Ramos, Sr.[1A], A. Germaná[2], C. Bonnin-Arias[1B], J. Navarro-Valls[1B], M. García-Ortega[1B], M. Pérez-Carrasco, Sr.[1C], J. Vega, Sr.[3].* [A]Neurocomputing & Neurorobotics, [B]Neurocomputing & Neurorobotics Group collaborator, [C]Optica II, Escuela Universitaria de Óptica, [1]Univ Complutense de Madrid, Madrid, Spain; [2]Universidad de Messina, Italy, Italy; [3]Department of Morphology and Cell Biology, Universidad de Oviedo, Oviedo, Spain.

771 — *A648* **Presynaptic Dystroglycan-pikachurin Complex Regulates The Proper Synaptic Connection Between Photoreceptor And Bipolar Cells.** *Fumiyuki Araki[1,2], Y. Omori[1,3], T. Chaya[1], S. Ueno[4], M. Kondo[5], S. Amano[2], T. Furukawa[1].* [1]Developmental Biology, Osaka Bioscience Institute & JST, CREST, Suita, Osaka, Japan; [2]Ophthalmology, University of Tokyo Graduate School of Medicine, Tokyo, Japan; [3]PRESTO, JST, Suita, Osaka, Japan; [4]Ophthalmology, Nagoya University Graduate School of Medicine, Nagoya, Japan; [5]Ophthalmology, Mie University Graduate School of Medicine, Tsu, Japan.

772 — *A649* **Cones Modify Their Frequency Tuning Curve In Response To Contrast Due To Membrane Properties.** *Marcus H. Howlett, M. Kamermans.* Retinal Signal Processing, Netherlands Institute for Neuroscience, Amsterdam, The Netherlands.

773 — *A650* **Spatial Statistics Of S-Cones In Primate/Human Retinal Periphery Suggests A Correlation With Domains Of Vascular Subtypes.** *Peter K. Ahnelt[1], J. Seng[2], M. Zieger[1,2], T. Hasegawa[2], O. Martinez Mozos[2].* [1]Dept. Neurophysiology, Medical University of Vienna, Vienna, Austria; [2]Dept. Advanced Information Technology, Kyushu University, Fac. Information Sci. & Electrical Eng., Fukuoka, Japan.

774 — *A651* **Expression Pattern of P2Y1 Purinergic Receptor on Intact and Injured Retinas of Zebrafish.** *Maria P. Faillace[1], A.G. Battista[2].* [1]Department of Physiology, School of Medicine, University of Buenos Aires and IQUIFIB-CONICET, Buenos Aires, Argentina; [2]Department of Physiology, School of Medicine University of Buenos Aires, Buenos Aires, Argentina.

775 — *A652* **On- And Off-ERG Responses Driven By L- And M-cones.** *Jan J. Kremers[1], G. Pangeni[2], N.R. Parry[3], D. McKeefry[4], I.J. Murray[5].* [1]Dept of Ophthalmology, University of Erlangen, Erlangen, Germany; [2]Ophthalmology, University Hospital Erlangen, Erlangen, Germany; [3]Vision Science Centre, Manchester Royal Eye Hospital, Manchester, United Kingdom; [4]School of Optometry and Vision Sciences, University of Bradford, Bradford, Uzbekistan; [5]Optometry & Vis Sci, FLS, Univ of Manchester, Manchester, United Kingdom.

776 — *A653* **Sirt3 Expression In Ocular Tissues Of Mouse.** *Norimitsu Ban[1A,1B], S. Miyake[1A], N. Takahashi[1A], K. Tsubota[1B], Y. Ozawa[1A,1B].* [A]Laboratory of Retinal Cell Biology, [B]Department of Ophthalmology, [1]Keio University, School of Medicine, Tokyo, Japan.

777 — *A654* **Mapping of Functional Consequence Sites in the Human Optineurin Gene.** *Sanja B. Turturro, H. Ying, X. Shen, R. Shyam, B.Y. Yue.* Ophthalmology and Visual Science, University of Illinois at Chicago, Chicago, IL.

778 — *A655* **Retinal Ganglion Cell Degeneration In The Senescence-accelerated Mouse.** *Yasunari Munemasa, Y. Kitaoka, K. Kojima, S. Ueno.* Ophthalmology, St Marianna University, Kawasaki, Japan.

779 — *A656* **Mechanisms of Glucose Protection of Cultured Rat Retinal Cells from Experimental Anoxia.** *Guoge Han[1,2], J.P. Wood[3], G. Childlow[3], T. Mammone[3], R.J. Casson[1].* [1]Department of Ophthalmology, University of Adelaide, Adelaide, Australia; [2]Department of Ophthalmology, Wuhan University, Renmin Hospital of Wuhan University, Wuhan, China; [3]Ophthalmic Research Laboratories, South Australian Institute of Ophthalmology, Australia.

780 — *A657* **Deimination Modulates Atp5b Mrna Transport In Retinal Ganglion Cells.** *Di Ding[1A,1B], M. Enriquez-Algeciras[1A], K.R. Dave[1C,1D], M. Perez-Pinzon[1C,1D], S. Bhattacharya[1A,1B].* [A]Ophthalmology, [B]Biochemistry, [C]Neurology, [D]Neuroscience Program, [1]University of Miami, Miami, FL.

781 — *A658* **Co-Relation Between Transcriptomic And Metabolomic Changes In The Axotomized Adult Rat Retina.** *Marta Agudo[1], F.M. Nadal-Nicolas[1,2], P. Sobrado-Calvo[2], M. Diaz-LLopis[3], M. Vidal-Sanz[2], J-L. Mullor[4].* [1]Unidad de Investigacion, Hospital Universitario Virgen de la Arrixaca, Murcia, Spain; [2]Dpto Oftalmologia, Universidad de Murcia, Murcia, Spain; [3]Universidad de Valencia, Hospital La Fe, Valencia, Spain; [4]Instituto de Investigación Sanitaria Hospital La Fe, Valencia, Spain.

782 — *A659* ***In Vitro* Evidence To Show That Blue Light Influences Mitochondrial Functions Negatively.** *Susana del Olmo-Aguado, N.N. Osborne.* Fundación de Investigación Oftalmológica, Instituto Oftalmológico Fernández-Vega, Oviedo, Spain.

783 — *A660* **Changes in Insulin Receptor Substrate 2 (IRS-2) Alter the Retinal Morphology and Dynamics in Relation to Diabetes Mellitus.** *Mara Albert[1], S. Pons-Vazquez[2], J.M. Romero[3], S. Sanz-Gonzalez[4A], D. Burks[4B], M.D. Pinazo-Duran[5].* [1]Ophthalmic Research Unit Santiago Grisol, University Hospital Dr Peset, valencia, Spain; [2]University Hospital Dr Peset, Ophthal Resrch Unit Santiago Grisolia, Valencia, Spain; [3]Biotechnology and Health Sciences, University of Alicante, Alicante, Spain; [A]Molecular endocrinology, [B]Molecular Endocrinology, [4]Research Center Principe Felipe, Valencia, Spain; [5]Ophthal Research Unit, University Hospital Dr Peset, Valencia, Spain.

784 — *A661* **Overexpression of CCR2 Gene Promotes Efficient Recruitment of Retinal Microglia.** *Xiaoshuang Jiang, Y. Ni, G. Xu.* Ophthalmology Department, Eye and ENT Hospital of Fudan University, Shanghai, China.

785 — *A662* **Alterations in the Barrier Function and Cell Migration in Stable RGC5 Cell Lines Induced by Expression of Wild-type and Mutated Myocilin.** *Hongyu Ying, X. Shen, B.Y. Yue.* Ophthalmology and Visual Sciences, Univ of Illinois at Chicago, Chicago, IL. TG

786 — *A663* **Angiopoietin-2 May Play A Role As Protective Factor In Sickle Cell Retinopathy.** *Monica B. Melo[1A], P.R. Cruz[1A], T.R. Zaccarioto[1B], F.N. Mitsuushi[1C], S.A. Pereira Filho[1C], R.P. Lira[1C], K.Y. Fertrin[1D], F.F. Costa[1D], J.P. Vasconcellos[1C].* [A]CBMEG, [B]Clinical Pathology, [C]Ophthalmology, [D]Hemocentro, [1]University of Campinas, Campinas, Brazil.

787 — *A664* **Igf-1/igf-1r System Implication In Proliferative Retinopathies.** *Valeria E. Lorenc[1], S.G. Ortiz[1], M.C. Sanchez[2].* [1]CIBICI-Dpto de Bioquimica Clinica, Facultad de Ciencias Quimicas UNC, Cordoba, Argentina; [2]CIBICI-Dpto de Bioquimica Clinica, Fac de Ciencias Quimicas UNC, Cordoba, Argentina.

788 — *A665* **Effect of Bevacizumab on Cell Cycle of VEGF- Enriched Proliferating Choroidal Endothelial Cells.** *Raluca Rusovici, C. Patel, K.V. Chalam.* Ophthalmology, University of Florida, Jacksonville, FL.

789 — *A667* **Acyclovir Attenuates Stress-Induced miRNA-146a Levels in Human Retinal Pigment Epithelial (RPE) Cells.** *James M. Hill[1A], C. Clement[1A], P.K. Mukherjee[2], J-G. Cui[1B], Y. Li[1B], S. Bhattacharjee[1C], H.E. McFerrin, Jr.[3], P.S. Bhattacharjee[3,1A], Y. Zhao[4], W.J. Lukiw[5].* [A]Ophthalmology, [B]Neuroscience, [C]Ophthalmology/Neuroscience, [1]LSUHSC, New Orleans, LA; [2]Neuroscience Cntr/Ophthalmology, LSU Health Sciences Center, New Orleans, LA; [3]Biology, Xavier University of Louisiana, New Orleans, LA; [4]University of Texas Health Sciences Center, Houston, TX; [5]Neuroscience & Ophthalmology, Lousiana State Univ Hlth Sci Ctr, New Orleans, LA.

undergo some apoptosis and, to a large extent, necrosis as a result of zinc chelation *in vivo*.
Conclusions: Photoreceptor release of ionic zinc with glutamate and zinc's action on presynaptic calcium channels has been shown. Here we show that chelation of *endogenous* zinc results in an increase of glutamate release, as evidenced by an increase in responses of the postsynaptic horizontal cells. *In vivo* zinc chelation likely removes inhibitory actions of zinc on photoreceptor glutamate release, leading to downstream excitotoxic damage to the inner retina. These observations suggest an important modulatory and neuroprotective role of ionic zinc at the photoreceptor terminal
Commercial Relationships: **Ivan Anastassov**, None; **Richard Chappell**, None
Support: NSF Grants 1026531 &1214162 and NCRR/NIH Grant RR003037 to RLC

Program Number: 769 **Poster Board Number:** A646
Presentation Time: 11:15 AM - 1:00 PM
Immunocytochemical Localization Of The Voltage-gated Calcium Channel α2δ4 Subunit In The Rodent Retina
Luis Perez de Sevilla Muller, Janelle Liu, Alex Solomon, Allen Rodriguez, Nicholas Brecha. Department of Neurobiology, UCLA University, Los Angeles, CA.
Purpose: Voltage-gated calcium channels are transmembrane proteins that mediate numerous neuronal functions such as the rapid influx of Ca^{2+}, transmitter release, gene transcription and synaptic plasticity. They are heteromultimeric channels consisting of an α1 subunit, and auxiliary $\alpha_2\delta_1$- $\alpha_2\delta_4$, and β subunits. Whereas some studies reported the presence of $\alpha_2\delta_{1-3}$ in the brain, the expression and localization of the $\alpha_2\delta_4$ accessory subunit in the rodent brain and retina remain unclear.
Methods: To determine the expression of the $\alpha_2\delta_4$ gene, we used RT-PCR from different tissues of mouse and rat with specific primers. The cellular localization of the $\alpha_2\delta_4$ subunit was studied by single and double immunostaining in rodent retinal slices using well characterized antibodies.
Results: We found $\alpha_2\delta_4$ mRNA in brain, retina, lung, liver, optic nerve and heart of mouse and rat. In the retina, we found $\alpha_2\delta_4$ subunit to be strongly localized in Mueller cells, including Mueller cell endfeet, putative displaced ganglion cells and in the outer plexiform layer, brightly fluorescent puncta consistent with their expression in rod bipolar cells and photoreceptor terminals.
Conclusions: This is the first study that shows the localization of the $\alpha_2\delta_4$ subunit in the mouse and rat retina.In conclusion, $\alpha_2\delta_4$ subunit may play regulatory roles in the ribbon synapses between photoreceptors and bipolar cells by modifying the properties of the channel.
Commercial Relationships: **Luis Perez de Sevilla Muller**, None; **Janelle Liu**, None; **Alex Solomon**, None; **Allen Rodriguez**, None; **Nicholas Brecha**, None
Support: by the U.S. Army Medical Research & Materiel Command (USAMRMC) and the Telemedicine & Advanced Technology Research Center (TATRC), at Fort Detrick, MD under Contract Number:W81XWH-10-2-0077

Program Number: 770 **Poster Board Number:** A647
Presentation Time: 11:15 AM - 1:00 PM
Acid-Sensing Ion Channels 2 And 4 (Asic2 Asic4) Are Regulated By Light In The Zebrafish Retina
Celia Sanchez-Ramos, Sr.[1A], Antonino Germaná[2], Cristina Bonnin-Arias[1B], Juan J. Navarro-Valls[1B], Marcos García-Ortega[1B], María Jesús Pérez-Carrasco, Sr.[1C], José Antonio Vega, Sr.[3]. [A]Neurocomputing & Neurorobotics, [B]Neurocomputing & Neurorobotics Group collaborator, [C]Optica II, Escuela Universitaria de Óptica, [1]Univ Complutense de Madrid, Madrid, Spain; [2]Universidad de Messina, Italy, Italy; [3]Department of Morphology and Cell Biology, Universidad de Oviedo, Oviedo, Spain.
Purpose: Acid-sensing ion channels (ASICs) are H+-gated cation channels that monitor deviations from the physiological values of extracellular pH. ASIC genes in zebrafish (zASICs) are expressed in the central nervous system and the retina. pH variations in the retina are thought to be involved in the fine-tuning of visual perception and in the adaptation of the retinal responses to different light intensities. Moreover, ASIC2 knock-out mice are also more sensitive to light-induced retinal degeneration. This study examines the effects of continuous light or darkness exposure in the mRNA levels and cell distribution of ASIC2 and ASIC4 in the retina of adult zebrafish.
Methods: We examined the retinas of adult zebrafish exposed to light-darkness rhythm, or to continuous light (10 days) or continuous darkness (10 days). Total RNA was extracted from retinas isolated from adult zebrafish. Levels of mRNA for the genes zASIC2a, zASIC2b and zASIC4 were determined by qRT-PCR, and the cell localization using immunohistochemistry.
Results: Detectable ASIC2a, ASIC2b and ASIC4 mRNA levels were detected in the adult zebrafish retina. The protein products of both ASIC2 isoforms were detected in the photoreceptor cells, pleximorm layers and ganglion cells layers and the optic fascicle; ASIC4 immunoreactivity was detected in the photoreceptor cells and ganglion cell layer. Continuous light exposure resulted in decrease levels of ASIC2 mRNs and the proteins were detected in the same cells as in control; ASIC4 mRNA levels were up-regulates and the intensity of immunainig as well. Continuous darkness exposure resulted in not changes neither in ASIC4 mRNA levels or protein expression, whereas down-regulates ASC2 mRNAs and the immunoreactivity was absent.
Conclusions: The variations in the expression of ASIC2 and ASIC4 genes and proteins after continuous light and darkness exposure demonstrate that they are regulated by light and suggest changes in the extracellular pH that must be regulated in these environmental conditions.
Commercial Relationships: **Celia Sanchez-Ramos, Sr.**, None; **Antonino Germaná**, None; **Cristina Bonnin-Arias**, None; **Juan J. Navarro-Valls**, None; **Marcos García-Ortega**, None; **María Jesús Pérez-Carrasco, Sr.**, None; **José Antonio Vega, Sr.**, None
Support: None

Program Number: 771 **Poster Board Number:** A648
Presentation Time: 11:15 AM - 1:00 PM
Presynaptic Dystroglycan-pikachurin Complex Regulates The Proper Synaptic Connection Between Photoreceptor And Bipolar Cells
Fumiyuki Araki[1,2], Yoshihiro Omori[1,3], Taro Chaya[1], Shinji Ueno[4], Mineo Kondo[5], Shiro Amano[2], Takahisa Furukawa[1]. [1]Developmental Biology, Osaka Bioscience Institute & JST, CREST, Suita, Osaka, Japan; [2]Ophthalmology, University of Tokyo Graduate School of Medicine, Tokyo, Japan; [3]PRESTO, JST, Suita, Osaka, Japan; [4]Ophthalmology, Nagoya University Graduate School of Medicine, Nagoya, Japan; [5]Ophthalmology, Mie University Graduate School of Medicine, Tsu, Japan.
Purpose: Dystroglycan (DG) is a key component of the dystrophin-glycoprotein complex (DGC) at the neuromuscular junction postsynapse. In the mouse retina, the DGC is localized at the presynapse of photoreceptor cells. We previously reported that an extracellular matrix protein, Pikachurin, is essential for the proper formation of ribbon synaptic structures. Pikachurin KO mice showed a reduced amplitude and prolonged implicit time of the b-wave similar to other mutant mice with perturbed DGC complex formation. Pikachurin physically interacts with DG, and proper glycosylation of DG is required for its interaction with Pikachurin. It was reported that the loss of DG in Muller glial cells causes ERG abnormality. However, the functional role of presynaptic DG in photoreceptor cells remains unclear.
Methods: To investigate DG function in the photoreceptor ribbon synapse, we ablated DG from photoreceptor cells by conditional gene targeting. To accomplish this, we mated the DGflox line with the Crx-Cre transgenic mouse line (DG CKO) in which Cre-mediated recombination occurs in both rod and cone photoreceptor precursors.
Results: We found that the DG CKO retina showed a reduced amplitude and a prolonged implicit time of the ERG b-wave. EM analysis revealed that bipolar dendrite invagination into the photoreceptor terminus is perturbed in the DG CKO retina. Interestingly, in the Pikachurin KO retina, the DG signal at the ribbon synaptic terminus was severely reduced, suggesting that pikachurin is required for the presynaptic accumulation of DG at the photoreceptor synaptic terminus. Furthermore, we found that overexpression of pikachurin induces formation and clustering of a DG-pikachurin complex on the cell surface. The Laminin G repeats of pikachurin, which are critical for its oligomerization and interaction with DG, were essential for the clustering of the DG-pikachurin complex as well.
Conclusions: These results suggest that oligomerization of pikachurin and its interaction with DG causes DG assembly on the synapse surface of the photoreceptor synaptic terminals. Our results reveal that the presynaptic interaction of pikachurin with DG at photoreceptor terminals is essential for both the formation of proper photoreceptor ribbon synaptic structures and normal retinal electrophysiology.
Commercial Relationships: **Fumiyuki Araki**, None; **Yoshihiro Omori**, None; **Taro Chaya**, None; **Shinji Ueno**, None; **Mineo Kondo**, None; **Shiro Amano**, None; **Takahisa Furukawa**, None
Support: CREST and PRESTO from Japan Science and Technology Agency, Grant-in-Aid for Scientific Research

Program Number: 772 **Poster Board Number:** A649
Presentation Time: 11:15 AM - 1:00 PM
Cones Modify Their Frequency Tuning Curve In Response To Contrast Due To Membrane Properties
Marcus H. Howlett, Maarten Kamermans. Retinal Signal Processing, Netherlands Institute for Neuroscience, Amsterdam, The Netherlands.
Purpose: In natural scenes light intensity and contrast are statistically independent. The visual system seems to utilize this phenomenon as adaptive mechanisms for luminance and contrast operate independently in many classes of visual neurons. Retinal luminance adaption begins at the photoreceptor level whereas retinal contrast adaption is believed to start at later stages of processing as cones have been reported not to adapt to contrast. However, we find that this might not be entirely the case.
Methods: Light responses of cone photoreceptors from isolated gold fish retina were recorded by whole cell voltage and current clamp techniques. Both naturalistic chromatic time series of intensities and monochromatic artificial time