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MEETING ABSTRACT

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$Ca_V1.4$ Ile745Thr mutation differently affects rod and cone visual pathways

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Background: $Ca_V1.4$ L-type calcium channels are predominantly expressed in retina where they are essential for glutamatergic release from photoreceptors (PRs) to bipolar cells (BCs) during transmission of light-evoked signals. Their importance is supported by the fact that mutations identified in the gene encoding $Ca_V1.4$ are associated with congenital stationary night blindness type 2 (CSNB2) in humans. Among all the mutations, patients carrying the mutation Ile745Thr (IT) presented with a severe CSNB2 phenotype including a drastic reduction in the ERG's b-wave that points to dysfunctional synapses between PRs and the BCs. The IT mouse models' ERG shows similar features and can therefore be considered a valid model to study CSNB2 and the role of $Ca_V1.4$ in the retina. In this study we investigated the BC visual pathways in this animal model to understand the mechanism underlying the pathogenesis of CSNB2.

Methods: By means of microelectrode array (MEA), we investigated the retinal output upon light stimulation of whole-mounted retinas of IT mice and wild-type (WT) controls. Photoreceptors were stimulated with full-field flashes of scotopic (rods-only) and photopic (cone-only) light delivered by a digital light projector. Their retinal morphology was examined immunohistochemically in retinal sections and whole-mounts.

Results: In IT retinae only 26% of the ganglion cells (GCs) responding to scotopic stimulation were also responsive to photopic light suggesting a major defect in the primary cone pathway (cone → cone BCs → GCs). Compared to WT mice the cone marker, cone arrestin showed abnormal arrangements of cones in whole-mount retinas and irregular formation of telodendria which are fine protrusions electrically connecting cones and rods. To test whether the electrical synapses were functional we directed the light signal only through the secondary rod pathway (rod → cone → cone BCs → GCs), by application of 50 µM L-AP4 or 2 µM strychnine. Using this pharmacological approach, we completely abolished the scotopic response in IT but not WT mice, suggesting that cones are more affected by the IT mutation, presumably due to a lack of cone-to-rod electrical signaling.

Discussion: Taken together, we showed a strong reduction of the cone-driven signal in the IT mouse model as inferred by the significant loss of photopic response. The communication failure between cones and rods, seen while pharmacologically isolating the secondary rod pathway, might be due to the increase of Ca^{2+} influx in the synaptic terminals. In fact, the gain-of-function nature of the IT mutation may lead to an increased Ca^{2+} influx that could cause a dysregulation of connexin. Why cones are more affected that rods in this animal model still remains an open question, but adds an important piece of information relevant also for future medical treatments.

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