Ectopic expression of mouse melanopsin in *Drosophila* photoreceptors reveals fast response kinetics and persistent dark excitation

The axons of the retinal ganglion cells in our eyes form the optic nerve. These neuronal cells are divided into two groups: image forming neurons, which are connected to the visual cortex and underlie image formation (~98% of the neurons) and non-image forming neurons, which are connected to the supra chiasmatic nucleus in the hypothalamus (~2% of the neurons). The latter small group calibrate by direct photic input the circadian pacemaker of the master circadian clock (the major biological clock that has many functions, including generation of jetlag) and support non-image forming (NIF) light dependent functions critical for our health. The neurons of the small group are called "intrinsically photosensitive retinal ganglion cells (ipRGC)" because they express the light activated melanopsin (OPN4) photopigment.

There are difficulties in advancing understanding of ipRGC phototransduction (the process in which the light is translated into electrical signals understood by the brain). The main obstacle is the scarcity of ipRGCs and the low expression levels of phototransduction proteins in these cells. This difficulty makes it nearly impossible to investigate phototransduction of the ipRGC by employing the same set of biochemical and electrophysiological approaches that proved successful in characterizing rhodopsin signaling processes in image forming rod and cones photoreceptor cells. Therefore, at present the knowledge of phototransduction of ipRGC is still fragmented. A promising way to characterize the OPN4 photopigment arises from the apparent similarity between phototransduction of ipRGC and the fly. It has been well established that several features of ipRGC photosensitivity are characteristic of *Drosophila* photosensitivity. However, a major difference is the extremely slow light-response kinetics of ipRGC, which is in sharp contrast to the fast kinetics of fly phototransduction. The slow kinetics of ipRGC prevents using melanopsin expressing retinal cells as a promising tool for visual restoration of the blind in most cases of human blindness.

In the present research we used transgenic *Drosophila*, in which the mouse OPN4 replaced the native Rh1 photopigment of *Drosophila* photoreceptors. Immunocytochemistry revealed OPN4 expression at the base of the rhabdomeres (the cell region that absorbs the light, see figure 1). Measurements of the Early Receptor Current (ERC), a linear manifestation of photopigment activation indicated large expression of OPN4 in the plasma membrane. Comparing the ERC amplitude and action spectra between wild type (WT) and the Opn4-expressing *Drosophila*, further indicated that mouse melanopsin was expressed. Strikingly, the light induced current (LIC) of the Opn4-expressing fly photoreceptors was ~40 folds faster than that of ipRGC (figure 2). This is the first demonstration of heterologous functional expression of mammalian melanopsin in the genetically emendable *Drosophila* photoreceptors. Moreover, the fast melanopsin-activated ionic current of *Drosophila* photoreceptors relative to that of mouse ipRGC, indicates that in contrast to the prevailing dogma, the slow light-response of ipRGC does not arise from an intrinsic property of melanopsin. Thus, the coupling of ectopically expressed melanopsin with the native signaling proteins of fly photoreceptors generates extremely fast phototransduction cascade, which can be very useful for
investigating the still unclear mechanism of melanopsin-activated phototransduction

A

OPN4 expressed in fly R1-6

B

Native OPN4 of ipRGC

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