

## 20. Sensory Cells: photoreceptor cell

The number of cells in the human body was estimated to be 36 and 28 trillion for males and females, respectively (e.g., Hatton, I.A., et al., PNAS, 120, 2023), which was previously thought to be 60 trillion. Although every cell in our body emerged from the differentiation of a round-shaped fertilized egg, their shapes and sizes are quite different in different organs. There is no doubt that different shapes are closely related to different cellular functions. Among them, the differentiation into neural cells is astonishing, and their shape is well known<sup>1)</sup>. However, the shapes of photoreceptor cells in our eyes or hair cells in the inner ear, and their importance for their functions are not popular. Here, we discuss shape, function, and brief molecular mechanisms of photoreceptor cells.

- 1) It is not difficult to understand why neurons in the brain show such specialized shapes if we know their functions. But if we are asked to show their shapes without any information other than a spherical fertilized egg, I am sure that we cannot reach the shapes we know. Nature has acquired this during evolution.

**Human photoreception:** We should know the characteristics and performance of human vision before discussing the shape and function of photoreceptor cells. The range of light intensities we experience spans 10 orders of magnitude, from the darkness of a night to the brightness of daylight at noon in midsummer. Our photoreceptor cells function in this wide range of light intensity.

An interesting question is how weak light we can detect. A research report combining a theory and experiments appeared in 1942, aimed at defining the minimum number of photons that we can report to “see” (Hecht, S., et al., J. Gen. Physiol., 1942). They assumed that the number of photons absorbed in the retina by a weak intensity of light should be Poisson distributed, and they calculated the detection probability. By comparing the theoretical curve of detection probability and the reported probability by human subjects, they concluded that we can detect photons as small as 6 absorbed in our retina. Since there are  $10^8$  photoreceptors in our retina, this leads to the conclusion that a single photoreceptor can detect a single photon.

There are photoreceptor cell rods and cones in our retina, which are named after their shape. Rods work in weak light at nighttime, with the capability of detecting one photon, but cannot discriminate color (wavelength). In contrast, cones work at daytime with the capability of detecting colors (red to blue, 780 – 380 nm) by three different cones.

**Shape and function of rods:** The intracellular structure of rods is specialized for detecting a photon (Fig.1). Since the front of the eyeball is lower in Fig.1, photons come from the bottom. There are 1,000 disk-shaped structures, called disks, which are stuck in the outer segment of a rod. Rhodopsin (Rh), a photon-detecting protein, is densely packed both in the upper and lower disk membranes. Thus, a photon can interact with a Rh in the outer segment. Since the probability for a photon to interact with a single Rh is below 1, this structure is suitable to detect a photon somewhere in the outer segment.

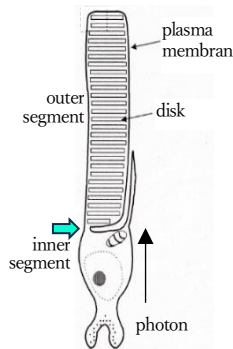


Fig.1 Structure of a rod

Photon-detection by a Rh, which causes photo-isomerization of Rh, triggers cascades of chemical reactions and finally closes cation channels in the outer segment. This closure of cation channels leads to a change in the membrane potential, which is transmitted to the brain through the presynaptic terminal of a rod, which is shown at the bottom of Fig.1. Thus, we recognize light.

**Molecular mechanism of photodetection by rods:** Here, a question arises: how is the photon-detecting signal transmitted to the plasma membrane from the disconnected disk where Rh<sub>s</sub> reside? There were discussions on this, where the cGMP hypothesis and the Ca<sup>2+</sup> hypothesis were competing. Both hypotheses are based on observations that both cGMP and Ca<sup>2+</sup> concentrations were changed by light stimuli. Finally, cGMP was proven to be a molecule directly responsible for regulating cation channels in the outer segment membrane using patch-clamp technology (Fesenko, E. E., et al., Nature, 1985). Ca<sup>2+</sup>, however, is shown to be involved in regulating the photon-detecting signal to cation channels, although it does not directly control these channels.

This is a typical example that the open discussion with evidence advances science. However, this is not always true. Discussions between Cajal, S. R. and Golgi, C. around 1900 are well known. They had opposing views on neurons. Cajal held the “Neuron Doctrine”, where the nervous system was constructed by many separate entities of neurons, while Golgi held the “Reticular Theory”, where the nervous system was a continuous single entity. Cajal and Golgi jointly won the 1906 Nobel Prize in Physiology or Medicine for their works on neurons and on Golgi staining, respectively. Despite this, both of them still showed a conflict in their Laureate Lectures. It is curious why Golgi held the “Reticular Theory”, because his staining was capable of showing a single neuron among many.

**Connecting cilium:** Connecting cilium (CC), shown by a green arrow in Fig.1, is a characteristic structure of photoreceptor cells. CC is a thin structure connecting the inner and outer segments, where microtubules run, on which Rh molecules and lipids synthesized in the inner segment are transported to the outer segment. There are many reports on this. However, why CC is a thin structure? If it is dedicated only to transporting molecules, thick CC should be better.

In the outer segment, the signal of photon detection by Rh is transmitted to ion channels in the plasma membrane. Chemical reactions here change the concentration of molecules associated with this transmission. To transmit this to cation channels on the outer segment quickly and unblurred, the change in the concentrations of cGMP, ions, and proteins on the way from Rh to cation channels should be prevented from escaping to other regions. Thin CC is ideal for this, because the spatial impedance for molecular diffusion is increased, acting CC as the diffusion barrier<sup>2)</sup>. Proteins and lipids synthesized in the inner segment are transported to the outer segment by motor proteins, compensating for the high spatial impedance in CC.

Modification of the spatial impedance of CC by experiment will be quite difficult or almost impossible, because side effects might occur if it is possible. 4D spatio-temporal simulation by A-Cell software, however, can show this possibility.

2) There is a report showing outer and inner segments are spatially segregated (Li, Y., et al., PNAS, 2020).