Journal of Advances in Science and Technology

Vol. 10, Issue No. 21, February-2016, ISSN 2230-9659

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AN INTERNATIONALLY INDEXED PEER REVIEWED & REFEREED JOURNAL

www.ignited.in

Journal of Advances in Science and Technology
Vol. 10, Issue No. 21, February-2016, ISSN 2230-9659

A Magic of CIS - Trans Isomerization and Light Induced Molecular Changes

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Abstract – When visible light hits the chromospheres (retinal), a p electron is promoted to a higher-energy orbital, allowing free rotation about the bond between carbon atom 11 and carbon atom 12 of the retinal molecule. About half the time, this rotation leads to the isomerization of retinal when the p electron returns to the lower-energy orbital. When retinal isomerizes, a conformational change in the protein opsin occurs. This conformational change initiates a cascade of biochemical reactions that result in the closing of Na^+ channels in the cell membrane. When the Na^+ channels are closed, a large potential difference builds up across the plasma membrane, and the potential difference is passed along to an adjoining nerve cell as an electrical impulse. The nerve cell carries this impulse to the brain, where the visual information is interpreted.

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INTRODUCTION

For most of us, vision is such an everyday occurrence that we seldom think to wonder how we are able to see the objects that surround us. Yet the vision process is a fascinating example of how light such as the light reflected off of the objects that we see can produce molecular changes with important consequences (i.e., our ability to perceive an image). The eyes receive the light and contain the molecules that undergo a chemical change upon absorbing light, but it is the brain that actually makes sense of the visual information to create an image. Hence, the visual process requires the intricate coordination of the eyes and the brain. How do these organs work together in order to allow us to see the light-reflecting objects around us as a visual image?

The vision process is initiated when photoreceptor cells are activated by light from an image. Hence, our discussion of the vision process shall focus on the photoreceptor cells, and how these cells are activated to generate a nerve impulse to the brain. The retina is lined with many millions of photoreceptor cells that consist of two types: 7 million cones provide color information and sharpness of images, and 120 million rods are extremely sensitive detectors of white light to provide night vision. (The names of these cells come from their respective shapes.) The outer segments (tops) of the rods and cones contain a region filled with membrane-bound discs, which contain proteins bound to the chromophore 11-*cis*-retinal. (A chromophore is a molecule that can absorb light at a specific wavelength, and thus typically displays a characteristic color.) When visible light hits the chromophore, the chromophore undergoes an isomerization**,** or change in molecular arrangement, to all-*trans*-retinal. The new form of retinal does not fit as well into the protein, and so a series of conformational changes in the protein begins. As the protein changes its conformation, it initiates a cascade of biochemical reactions that result in the closing of Na^+ channels in the cell membrane. Prior to this event, Na^+ ions flow freely into the cell to compensate for the lower potential (more negative charge) which exists inside the cell. When the Na^+ channels are closed, however, a large potential difference builds up across the plasma membrane (inside the cell becomes more negative and outside the cell becomes more positive). This potential difference is passed along to an adjoining nerve cell as an electrical impulse at the synaptic terminal**,** the place where these two cells meet. The nerve cell carries this impulse to the brain, where the visual information is interpreted.

THE VISION PROCESS FOR MONOCHROME VISION

The sequence of events to generate a signal to the brain for monochrome vision (which occurs in the rod cells) and for color vision (which occurs in the cone cells) is essentially the same, although monochrome vision is somewhat simpler. Hence, we shall first describe how a monochromatic visual nerve impulse is generated, and then show how color vision differs. The process of generating a monochromatic visual signal can be broken down into three important steps:

(I) Isomerization of Retinal

The first step in the monochrome vision process, after light hits the rod cell, is for the chromophore 11-*cis*-retinal to isomerize to all-*trans*-retinal. This event is best understood in terms of molecular orbitals, orbital energy, and electron excitation. When an atom or molecule absorbs a photon, its electrons can move to higher-energy orbitals, and the atom or molecule makes a transition to a higher-energy state. In retinal, absorption of a photon promotes a p electron to a higher-energy orbital (a p-p* excitation). This excitation "breaks" the p component of the double bond, thus allowing free rotation about the bond between carbon atom 11 and carbon atom 12 (see figure). Thus, when 11-*cis*-retinal absorbs a photon in the visible range of the spectrum, free rotation about the bond between carbon atom 11 and carbon atom 12 can occur and the all-*trans*-retinal can form. This isomerization occurs in a few picoseconds (10^{-12}s) or less. Energy from light is crucial for this isomerization process: absorption of a photon leads to isomerization about half the time; in contrast, spontaneous isomerization in the dark occurs only once in 1000 years! The molecule resulting from the isomerization is called all-*trans*-retinal. In the *cis* configuration, both of the attached hydrogens are on the same side of the double bond; in the *trans* configuration, the hydrogens are on opposite sides of the double bond. (As you can see in Figure) the *cis-trans* isomerization causes the conjugated carbon chain (alternating double and single bonds) to become straightened, and increases the distance between the -CH_3 group attached to carbon 5 and the oxygen at the end of the chain.

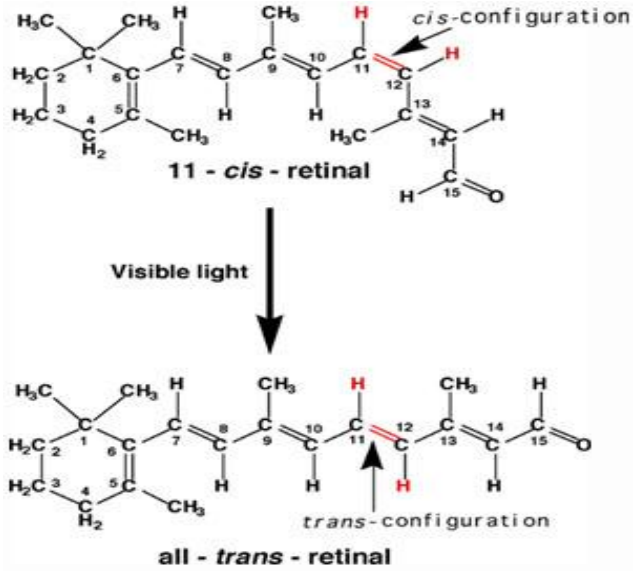

Fig. 1 : Conformational Changes 11 –cis –retinal to all –trans-retinal

(II) *Protein Conformational Changes Following Retinal Isomerization:*

The isomerization of retinal has an important effect on special proteins in the rod cell: the isomerization event actually causes the proteins to change their shape. This shape change ultimately leads to the generation of a nerve impulse. Hence, the next step in understanding the vision process for monochrome vision is to describe these proteins, and how they change their shape after retinal isomerizes.

In rod cells, the protein which binds the chromophore retinal is opsin, and the bound complex of 11-*cis*-retinal plus opsin is known as rhodopsin, or visual purple. Alone, 11-*cis*-retinal has a maximum absorbance in the ultraviolet part of the spectrum, but the maximum absorbance for rhodopsin is 500 nm (in the visible green part of the spectrum). Recall from the inorganic-synthesis experiment that the observed color of a substance is actually the complementary color to the color that is absorbed). Thus, the name "visual purple" describes the complementary color for rhodopsin. (Rhodopsin also absorbs in the ultraviolet region of the spectrum. However, the lens of the eye absorbs ultraviolet light, preventing it from reaching rhodopsin in the retina. This is why we cannot see ultraviolet light.) Opsin consists of 348 amino acids, covalently linked together to form a single chain. This chain has seven hydrophobic, or water-repelling, alpha-helical regions that pass through the lipid membrane of the pigment-containing discs.

This region consists primarily of nonpolar amino acids, which do not attract the polar water molecule. The chromophore is situated among these alpha helices in the hydrophobic region. It is covalently linked to Lysine 296, one of the amino acids in the opsin peptide chain.

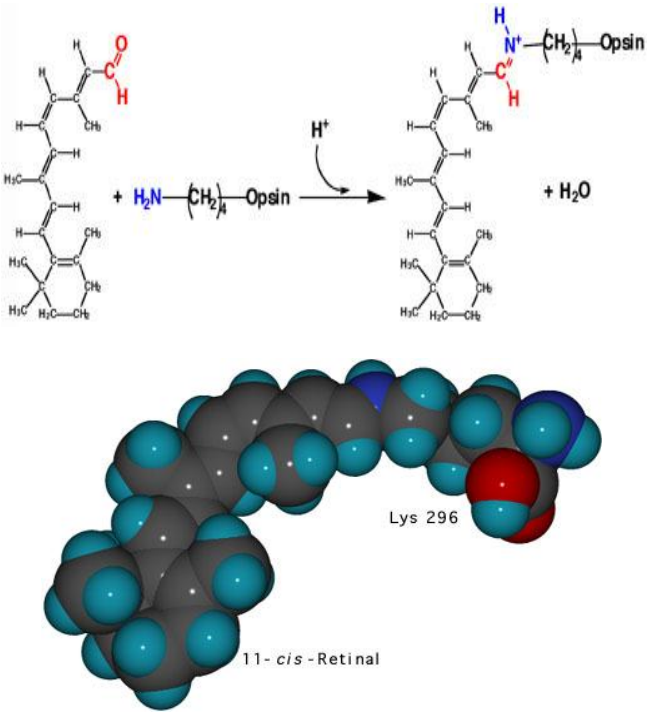

Fig.2.The upper panel is a two-dimensional representation of the reaction which links 11-*cis*-retinal to opsin. The lower panel is a three-dimensional close-up of Lysine 296 covalently attached to 11-*cis*-retinal.

When the chromophore absorbs a photon it isomerizes to the all-*trans* configuration without (at first) any accompanying change in the structure of the protein. Rhodopsin containing the all-*trans* isomer of retinal is known as bathorhodopsin**.** However, the *trans* isomer does not fit well into the protein, due to its rigid, elongated shape. While it is contained in the protein, the all-*trans chromosphere* adopts a twisted conformation, which is energetically unfavorable. Therefore, a series of changes occurs to expel the chromophore from the protein.

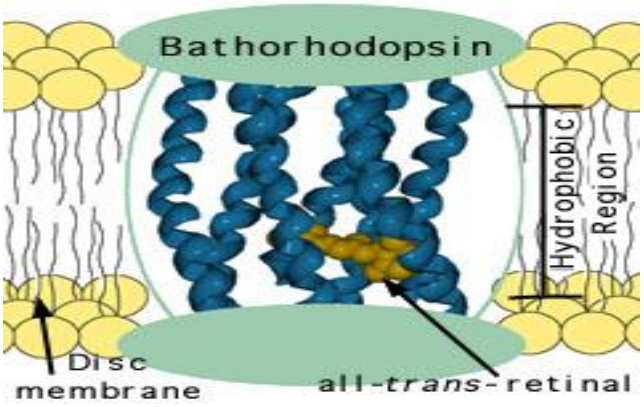

Fig. 3. schematic diagrams of rhodopsin (11-*cis*-retinal bound to opsin) and bathorhodopsin (all-*trans*-retinal bound to opsin) in the membrane of a pigment-containing disc in the rod cell.

Although the initial isomerization occurs without any change in the shape of the opsin protein, the twisted conformation of all-*trans*-retinal in bathorhodopsin is too unstable to remain in this configuration for long. Within nanoseconds (10^{-9} s), the shape of the protein begins to change. Ultimately, the all-*trans*-retinal molecule is expelled from the protein, yielding free opsin plus free all-*trans*-retinal. A series of intermediate complexes have been isolated at low temperatures, each absorbing maximally at a different wavelength. The names and characteristic l_{max} values for these intermediates are shown in Table 1.

(III) **Signal Transduction Cascade to Generate a Nerve Impulse**

After the metarhodopsin II is formed, there are approximately four more steps in the vision process: activation of the enzymes transducin and phosphodiesterase, hydrolysis of cyclic GMP, closing of Na^+ channels, and propagation of an electrical impulse to the brain. Recall, for a signal to be sent via a nerve fiber, the Na^+ channels must be closed so that a large charge difference across the rod's outer membrane builds up. (Recall the plasma membrane shown in Figure 3.) Once a large charge difference occurs, the membrane is said to be hyperpolarized. Then, charge travels as an electrical impulse down the rod cell to the synaptic terminal, where it is transferred to an adjoining nerve cell. How does this charge buildup occur?

The starting point for this process is the production of metarhodopsin II, as described above. This initiates the following cascade of events: First, metarhodopsin II complexes with the enzyme transduction and activates it. Transduction in turn activates another enzyme, phosphodiesterase. Phosphodiesterase catalyzes the hydrolysis of cyclic GMP.

Cyclic GMP is required to open Na^+ channels in the plasma membrane. In the dark, cyclic GMP is abundant and these channels stay open. Sodium cations enter freely into the rod cell, because the cell typically has a lower potential (is more negative) than the external environment, thus attracting the positively-charged ions. However, when cyclic GMP is hydrolyzed (gains an H_2O and breaks a bond) by the now-activated phosphodiesterase, it is no longer available to keep the Na^+ channels open. Sodium cations can no longer enter the cell freely, and so the cell's potential suddenly becomes even lower relative to the external environment. A large charge difference across the membrane is built up; this is known as hyper polarization**.** The large potential difference travels as an electrical impulse down the rod cell to the synaptic terminal, and is then transferred to an adjoining nerve cell. The nerve cell carries this impulse all the way to the brain. The brain then determines where the nerve impulse originated, and interprets the image.

COLOR VISION

Now that we have studied the vision process for monochrome vision, we can turn our attention to color vision. Recall that the nerve signals for color vision are generated in the cone cells. Color vision in the cone cells operates by essentially the same process as the monochrome vision in the rod cells. However, whereas the eye only has one type of rod cell, the eye has three different types of cone cells. The differences between the three types of cone cells, as we shall see below, allow us to distinguish colors.

Our color vision is trichromatic, *i.e.*, we perceive color through three fundamental receptors: red-absorbing, green-absorbing, and blue-absorbing cone cells. Each color in the visible spectrum can be made by a mixture of these three primary colors recognized by the three types of cone cells. Each type of cone cell contains a different protein bound to 11-*cis*-retinal and has its own characteristic absorption spectrum, corresponding to the particular pigment protein that it contains. Each absorbs maximally at a characteristic wavelength, but the absorbance peaks are rather broad and extend over a range of wavelengths. Therefore, some wavelengths are absorbed (to varying degrees) by more than one type of cone.

Orange light, for instance, is absorbed by both the green- and red-absorbing pigments, but the latter pigments absorb the orange light more efficiently. When the brain receives the combination of signals from the green- and red-absorbing cones, it interprets this as orange light. The combination would be different for yellow light (more green relative to the red absorbance). The three pigment proteins for color vision are similar to rhodopsin, and contain much of the same amino-acid sequence as rhodopsin. Only a few amino acids located near the retinal binding site are varied in these proteins. The absorption spectra of the red- and green-absorbing proteins are tuned by the presence of amino acids containing a hydroxyl (-OH) group near the retinal binding site. Recall that the alpha helices where retinal binds are hydrophobic composed of nonpolar amino acids. The hydroxyl group is a polar group (consider the relative electronegativities of oxygen and hydrogen), and therefore more attractive to water. It has been shown that replacement of a nonpolar amino acid with a polar amino acid at certain key positions shifts l_{max} about 10 nm to longer wavelengths (lower energy). The red and green proteins have more of their amino acid sequence in common than either does with the blue protein. Therefore, their absorption spectra are similar, whereas the absorption spectrum of the blue-absorbing pigment is more distinct.

CONCLUSION

Vision is a remarkable process by which we are able to interpret an image from light the eyes receive from the objects around us. Although this process depends on the interplay of many different factors including the optics of the eye, the isomerization of retinal, nerve impulses, and the brain's ability to reconstruct the image. Vision is fundamentally based on the change in the molecular orbitals of retinal that occurs when the molecule absorbs energy in the form of light reflected off of the objects that we see. Recall that when visible light hits the chromospheres (retinal), a p electron is promoted to a higher-energy orbital, allowing free rotation about the bond between carbon atom 11 and carbon atom 12 of the retinal molecule. About half the time, this rotation leads to the isomerization of retinal when the p electron returns to the lower-energy orbital. When retinal isomerizes, a conformational change in the protein opsin occurs. This conformational change initiates a cascade of biochemical reactions that result in the closing of Na^+ channels in the cell membrane. When the Na^+ channels are closed, a large potential difference builds up across the plasma membrane, and the potential difference is passed along to an adjoining nerve cell as an electrical impulse. The nerve cell carries this impulse to the brain, where the visual information is interpreted.