Physical aspects of sensory transduction on seeing, hearing and smelling

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What is the general principle of sensory transduction? Sensory transduction is defined as energy transformation from the external world to the internal world. The energy of the external world, such as thermal energy (heat), electro-magnetic energy (light), mechanical energy (sound) and the energy from molecules (chemicals), is converted into electrochemical events in the animal nervous system. The following five classes of special sense receptors are utilized for energy conversion: vision (photo); audition (sound); taste and smell (chemo); and tactile (mechano). There are also other special sense receptors, including thermo and noxious receptors. The focus of this study is on photoreceptors, sound-receptors and odorant-receptors because the transduction mechanisms of these receptors are explained biochemically and understood by a common physical principle; these biochemical models are well known in neuroscience. The following notable problems are inherent in these biochemical models: the cGMP ionophore model of the vertebrate photoreceptor cannot explain the fast photoresponse (~msec); the tip links connection model of stereocilia in the basilar membrane for opening the K⁺ channel on the tip of a hair has difficulty explaining the high frequency vibration of hair cells without a damping of the oscillation, and the odorant shape-specific receptor model for olfactory transduction has difficulty in discriminating the minute differences among similar fragrant smells of essential oils with different molecular shapes. These difficulties might arise from a lack of the physical sense when the transduction models were proposed. This article will reconsider these problems and propose rational models for visual, olfactory and auditory transduction.

Key words: vibration theory, ciliary cells, second messengers

The purpose of this article is to examine the similarities and differences in the underlying mechanisms of transduction in the sensory receptors for vision, olfaction and hearing. Light, sound and molecular vibration in odorant molecules have characteristic oscillation frequencies (wavelengths). In the case of light, the visible wavelength from near UV (ultra-violet) to near IR (infra-red) corresponds to 400 nm (7.5×10¹⁴ Hz) to 750 nm (4.0×10¹⁴ Hz), respectively. The human audible wavelength is approximately 17 m (20 Hz) to 1.7 cm (20×10³ Hz), assuming that sonic speed is 340 m/s. A photon with a wavelength of 500 nm has a quantal energy of 57 kcal/mol, and an acoustic phonon at a frequency of 10 kHz has a quantal energy of 3×10⁻⁶ cal/mol. In the case of olfaction, the binding energy of an odorant molecule to a receptor was estimated as 3.9~10.5 kcal/mol. In this connection, the noise level at room temperature, kT, is approximately 0.57 kcal/mol, which is lower than that of vision and olfaction but higher than that of hearing. Especially for color vision, we have three types of cones with specific maximum absorption characteristics for blue light, (λmax: 445 nm), green light, (λmax: 535 nm) and red (orange) light, (λmax: 570 nm). For sound reception, we have one long resonance plate (the
basilar membrane) corresponding to different frequencies of sound waves. In the case of odorant reception, Turin recently proposed a “vibration theory (spectroscopic theory)” instead of the structure-odorant relation theory that was proposed in 1996, and his hypothesis has developed during the last 20 years. Vibration appears to be the common signal in sensory transduction, although the frequencies for each case are different.

If vibration is the common signal in sensory transduction, there must be a common mechanism among visual, sound and odorant signal transduction; however, each has a different converter system dependent on each frequency. In the case of the high frequency vibration (4~7.5×10^14 Hz) of a visual signal, which converted directly to the chemical signals such as cis-trans conversion of rhodopsin and eventually the signals activated phosphodiesterase (PDE), that in turn decease cGMP concentration in the disc membrane. The middle range frequency of molecular vibration such as the Raman vibration, sensory transduction will depend on common types of receptors on the disc membrane of the rod (or cone) photoreceptors and on the chemosensory hair cells. In these cases it is reasonable that the vibration energy of photons and phonons are converted to the IP_3 (inositol trisphosphate) second messenger concentration from 0.1 to 3.0 μM^{3–5} and/or the cAMP (cyclic adenosine monophosphate) concentration from 10 to 200 μM^{6–8} in the receptors at the membrane. There are different types of sound energy; for example, mechanical pressure deforms the hair cell membrane, which is converted to membrane potential changes. In this case we focus attention on the lateral line organ (chemo-receptor) of a tadpole that is converted to a mechano-(sound) receptor after the tadpole metamorphoses into a frog. This metamorphic change will provide information showing that mechano- and chemo-receptors have a common ancestor and thus have a similar transduction mechanism. Generally, sensory receptors of light, sound and smell must have a common type of receptor structure, specifically ciliary cells, as shown in Figure 1. The cilia are formed through an unmyelinated process and are several micrometers long with a tubular structure of 0.1–0.2 μm in diameter. For example, inside the stereocillum are many actin filaments to support the hair structure, which lead to a significant amount of bound water (not free water) in the sensory hair cells.

The concept of a cell as a membrane bag of liquid was totally changed when Ling published his monograph titled “A physical theory of the living state” in 1962. Ling proposed that most of the water inside a cell was polarized in multilayers on protein surfaces and was an extremely scarce solvent environment for ions. Fifty years later his concept has gradually become established; however, experimental evidence to support his concept is not sufficient to provide an exact representation of the cell machinery. In this review, we will try to combine the ciliary cell model and the bound water model into a novel model of sensory transduction for vision, smell and hearing. The established molecular mechanism of transduction in different sensory receptors can be divided into direct and indirect activating receptor channels. In photoreception and chemoreception, the sensory stimulus modulates the flow of the receptor current by a second messenger pathway, whereas in directly activated transduction as by a mechanoreceptor, the stimulus drives directly to the gating of the ion channel.

Figure 1 Rough sketch and functional illustrated schemes of ciliary cells for sensory transduction, the upper and lower functional illustration showed un-stimulated state and stimulated state, respectively. (a) Vertebrate photoreceptors; cone (left) and rod (right), (b) Hair cells of vertebrate sound transduction, (c) Hair cells of vertebrate odor transduction.
Photo transduction mechanism of vertebrate and invertebrate photoreceptors

A. Classic model of photo transduction

Photo-transduction occurs in a three-stage process. First, a pigment, rhodopsin, absorbs a photon and is isomerized. Second, the isomerization triggers a biochemical cascade. Finally, the sodium currents are altered, modulating the ionic current within the receptor. In stage 1, the photo-excited rhodopsin (R*) binds to transducin (T) and facilitates the exchange of a bound GDP to GTP. This action leads to a release of the α subunit of T, which activates a cyclic GMP-phosphodiesterase (PDE) within 1 ms; thus, the internal cGMP concentration decreases for the vertebrate rod as shown in Figure 2 (a).

Under dark conditions, photoreceptors have a resting membrane potential of approximately −40 mV, which is caused by the dark current carried by Na⁺ and K⁺. Na⁺ enters the outer segment through the cGMP-gated Na⁺ channel that remains open as long as cGMP binds to the channel. In the scotopic condition, the continuous inward Na⁺ current depolarized the cell to be −40 mV. Photoreceptors are maximally depolarized or excited in the dark state. This steady depolarization continuously drives K⁺ out of the inner segment through voltage-dependent K⁺ channels. Through the inner and outer segments of the rod, Na⁺ flows into the rod through the cGMP-gated Na⁺ channel, whereas K⁺ goes out of the rod through the voltage-dependent K⁺ channel; thus, the electrical circuit is complete under dark conditions in the scotopic condition. During this dark state, Na⁺ and K⁺ are in equilibrium because of the activation of the Na⁺/K⁺-exchanging pump. Light striking the photo pigments decomposes rhodopsin, leading to a decrease in the rod membrane conductance for Na⁺ in the outer segment of the rod. This change causes hyperpolarization of the entire rod membrane. In photoreceptors, the average density of these channels in the outer segment is on the order of 600 μm⁻²; therefore, each rod contains at least 100,000 channels. A single R*(all-transform) causes activation of the G protein at a rate of approximately 1000−5000 G*/s at room temperature. The activated PDE hydrolyzes cGMP at a rate of 1000−4000 molecules/s. Light triggers a decrease in the cGMP concentration, leading to the closure of the cGMP-gated Na⁺ channels in the plasma membrane and hence to a reduction in the circulating current of the cell.

In some respects, the cone is comparable to a light-adapted rod, exhibiting a desensitized and accelerated response. There are major differences. In particular, the cone is much noisier than the rod, and its response does not saturate at a high intensity of steady illuminations as with the response of the rod. In the COS (cone outer segment), the structure of the ciliary membrane has a small diameter and long length, as shown in Figure 1. The diffusion constant for cGMP was estimated to be 50−196 μm²/sec in the intact ROS of a salamander, which is fast enough if photon triggers cGMP elevation to open channel (positive messengers). In the case of ROS and COS, however, decreasing signal of cGMP (negative messenger) must reach to already opened transduction channel then close it. Estimation of diffusion constant of negative messenger was never performed yet. Furthermore application of PDE to a piece of retina from dark adapted toad (Bufo marinus) did not decrease light responses (Yau et al., private communication and unpublished data). Therefore it is not so easy to determine exact mechanism for vertebrate
transduction in ROS and COS.

B. Ca\(^{2+}\) as a 2nd messenger model for vertebrate phototransduction

In 1975, Hagins and Yoshikami proposed that Ca\(^{2+}\) stored in the disc membrane was released and diffused to reach the Na\(^+\) channel and that the Ca\(^{2+}\) then closes the channel\(^{14}\). Although the Ca\(^{2+}\) elevation could not be observed, their model is attractive than that of cGMP because Ca\(^{2+}\) can reach the Na\(^+\) channel in the plasma membrane by the Ca\(^{2+}\) wave associated with the proton transfer along the surface of the bound water on the disk membrane, which will be described in detail in the next paragraph. In the case of PIP\(_2\) and IP\(_3\)R (the IP\(_3\) receptor), which are distributed on the disk membrane, photo irradiation breaks PIP\(_2\) down to produce Ca\(^{2+}\) in the disk membrane. This finding was demonstrated by the ultra-structural observations that the distribution of PIP\(_2\) stained with gold particles decreased during the light adaptation process in the rod outer segment\(^{15}\). The localization of IP\(_3\)R1 on the outer segment was established\(^{16}\). Is this finding compatible with Ca\(^{2+}\) and cGMP as second messengers in the ROS (rod outer segment)?

Using a positive feedback model, Yaroslavskiy et al. proposed that cGMP promotes PKG (protein kinase G) activity, which suppresses IP\(_3\)R activity by phosphorylation; thus, the activation of PDE is positively implicated in the Ca\(^{2+}\) signaling model\(^{17}\). The last question of this model concerns the mechanism by which Ca\(^{2+}\) rapidly blocks Na\(^+\) channel conductance. This mechanism should be well understood if the Ca\(^{2+}\)-activated K\(^+\) channel is involved, although it has not been identified on the disk membrane of the vertebrate retina.

C. IP\(_3\) as second messengers in invertebrate phototransduction

There is abundant evidence that PIP\(_2\) hydrolysis is involved in invertebrate phototransduction via the rhabdomeric membrane in Limulus\(^{18,19}\), squid\(^{20,21}\), Drosophila\(^{22,23}\) and Hermissenda\(^{24}\), as shown in Figure 2 (b). It is well known that invertebrates share two visual systems, a rhabdomeric photoreceptor and a ciliary photoreceptor. During evolutional development, they have differentiated into ocular photoreceptors and dermal photoreceptors. In this review, we focus on the ocular photoreceptor. A brief injection of IP\(_3\) into an ocular photoreceptor mimicked the quantal light responses (quantal bump), and the IP\(_3\)-induced Ca\(^{2+}\) release resulted in membrane depolarization in the Limulus ventral photoreceptor\(^{25}\) by activating the Ca\(^{2+}\)/Na\(^+\) exchange\(^{26,27}\).

A number of unexplainable findings were observed that opposed this exchange model, which may arise from the assumption regarding whether Ca\(^{2+}\) diffusion constant is fast enough to produce a photo-response after light illuminations. Assuming that IP\(_3\) is a second messenger, Sakakibara et al. injected IP\(_3\) into a Hermissenda type B photoreceptor and found that the response of the IP\(_3\) injection was consistent with the light response shown in Figure 3 (a)\(^{28}\). The responses to the injection of other types of second mes-

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**Figure 3** Light and 2nd messenger candidates induced response in the type B photoreceptor of invertebrate gastropoda *Hermissenda crassicornis* (adopted from Sakakibara et al., 1998). (a) Photoreceptor response to a flash of light (upper) and an IP\(_3\) injection (lower) with same duration, (b) responses to a light irradiation (upper), a cGMP injection (lower). Note that the response latency was quite different; the latency of cGMP injection was faster to be effective than that of light flash.
senger candidates were examined as follows: \( \text{Ca}^{2+} \), cAMP and cGMP were injected into the type B photoreceptors in *Hermisenda*, and there was no observable response to the \( \text{Ca}^{2+} \) injection, a train of action potential for the cAMP injection and a transient depolarization for the cGMP injection. As shown in Figure 3(b), the latency of the cGMP induced response was found to be inconsistent with the light response, with a slightly shorter increasing time (~0.5 sec) than that of light (~1.0 sec). What is a transduction channel for the invertebrate eye? According to numerous findings from research on *Drosophila* and *Limulus*, it is quite likely that the IP\(_3\) production from PIP\(_2\) hydrolysis via the activation of PLC (phospholipase C) by light irradiation is a first step. Although there are two candidates for the opening of the channels; the first involves intracellular IP\(_3\) opening the SOC (store-operated calcium channel)\(^{29}\), and the second involves IP\(_3\) evoking the TRP (transient receptor potential) channels\(^{30,31}\). Since we have known that brief \( \text{Ca}^{2+} \) injection did not modulate photoresponse at all in *Hermisenda* photo-receptor as mentioned above we could rule out the contribution of \( \text{Ca}^{2+} \) as a second messenger. Another possibility is the involvement of the TRP channel because the TRP responses in the *Drosophila* eye completely disappeared when the PLC was knocked out, as in the norpA mutant\(^{23}\), in which Na\(^+\) was shown to be the current carrier. The TRP channel involved in photo-transduction has not been identified; however, the TRPC for invertebrates\(^{26}\) and TRPM for vertebrates\(^{32}\) are promising. *Hermisenda* photoresponse showed a notably similar photoresponse to that of the vertebrate photo-receptor; a cGMP injection induced depolarized transient membrane potential responses in a dose-dependent manner\(^{28}\). This evidence shows that even an invertebrate photoreceptor possesses a cGMP-evoked Na\(^+\) channel, although it is insensitive to light.

### Ca\(^{2+}\) wave model associated with a proton current along a linear chain of water molecules in a ciliary cell

#### A. Diffusion of a second messenger in the cell

According to the observed values, the diffusion coefficient for cGMP and \( \text{Ca}^{2+} \) in the extracted cytosol were estimated as 150\( \mu \text{m}^2/\text{sec} \) and 15\( \mu \text{m}^2/\text{sec} \), respectively. In the case of \( \text{Ca}^{2+} \), for example, the observed value is much lower than that in free water (~1000\( \mu \text{m}^2/\text{sec} \))\(^{33}\). Another blow that diffusion coefficient value in cytosol experiment is that water in the extracted cytosol will be changed from bound water to free water with the elapsed time. The actual diffusion constant of cGMP in the free water was unable to find out. The estimated values were obtained by a suction electrode, which held an isolated ROS supplied with cGMPs at the tip of the electrode. Although the values of the diffusion constant were obtained from the diffusion equation, it must be paid attention that the calcium diffusion constant could not be calculated from the \( \text{Ca}^{2+} \) sensitive dye experiment, as discussed below.

#### B. Water state in the cell

According to a recent review by Mentre\(^{34}\), most biological and/or medical scientists could not perceive that the interior of a cell is occupied by an overcrowding huge macromolecule before the finding by Goodsell\(^{35}\).

Most neuroscientists, excluding electron microscopists, appeared to misunderstand the images of cytoplasm floating in a dense electron-transparent medium surrounded by abundant bulk water. Keith Porter named these structures micro-trabecules\(^{36}\). Based on these findings, very few biologists theorized that cell water could be different from general bulk (free) water. Bulk water is a good solvent and an ideal medium for diffusion. The collective evidence has frequently demonstrated that ions and small molecules can reach their target by diffusion into the cytoplasm because there might be a large quantity of bulk water. As was proposed by Goodsell, however, there is little space between the macromolecules\(^{35}\). It is reasonable to consider that macromolecules constitute mechanical obstacles for ionic diffusion. Their surfaces are patchworks of polar and apolar domains that can bind ions and polar molecules. We hesitate to conclude that such a complex and fast cell process can depend on the diffusion process.

#### C. Proton current along the bound water surface

Water molecules have electric dipoles. At the contact with macromolecules, these dipoles arrange themselves into a regular and very constructed manner, closely reflecting the patchwork of the macromolecular surface domain, hydrophobic or hydrophilic\(^{14}\). When water molecules are bound to consecutive polar amino acids (Asn, Cys, Gln Ser, Thr, Tyr) in a polypeptide chain, they can bind to form H-bonded lines. These lines of water molecules are a good conductor of protons, not of electrons. Accordingly, the calcium- or phosphate- ions in the transduction cascades, protons do not migrate along the water chain; they move by a successive flip-flop step from the first water molecule to the last water molecule of the chain. The entering proton does not move further than the first water molecule of the chain, and the last step of the outgoing proton is provided by the last water molecule of the chain. This process is a proton wave, and this domino-like wave motion is more rapid than diffusion\(^{37}\). The calcium wave observed in the living cell is always accompanied by a proton-wave/proton-transfer-signal which is more rapid than diffusion as mentioned above, because proton wave is transferred according to Coulomb interaction on the water surface. It is reasonable to assume that \( \text{Ca}^{2+} \) might be a good candidate as a 2\(^{nd}\) messenger even in vertebrate visual transduction. There is a very narrow space in the bulk water under the plasma membrane for negative charged IP\(_3\) and cyclic nucleotides. As a tentative conclusion, when light strikes the vertebrate photoreceptor, \( \text{Ca}^{2+} \) is released from the internal \( \text{Ca}^{2+} \)-store into the ROS and transferred to the plasma membrane quickly by the water molecule; the \( \text{Ca}^{2+} \) activates the \( \text{Ca}^{2+} \) activated K\(^+\) channel.
and causes hyperpolarized responses from the resting membrane potential (~40 mV). When light illuminates the invertebrate eye, IP_3 is released from the photoreceptor membrane, and it diffuses in the narrow gap of bulk water to activate the TRP channel, which causes depolarization by the entry of Na⁺.

Sound transduction induced by a vibrating hair cell in the ear

A. Disadvantage of the tip-link model

Mechano-transduction in a human inner-ear hair cell corresponds to a frequency range of 20 Hz to 20 kHz. A hair cell can transform vibrational energy into an electronic signal and can detect movement of atomic-scale dimensions with a rapid adaptation, as was described in a textbook.  

The geometry of the structures surrounding the hair cells ensures that the external physical stimulus is delivered to the hair cell as a displacement stimulus such as tympanic membrane vibration and bony structure vibration. Incoming sound initiates a travelling wave in the basilar membrane of the mammalian cochlea, whose amplitude peaks at a position dependent upon the sound frequency. The stereocilia of the hair cells located at the site of the peak traveling on the basilar membrane are deflected as a result of the geometry of the organ of Corti. This transformation system includes low noise amplification and spectral decomposition of incoming sound. To accomplish such transduction, mammalian cochlea rely on the harmonizing action of many hair cells. The organ of Corti within the cochlea contains the following two classes of hair cells: the inner hair cells, which act as sensory cells for the auditory nerve and the outer hair cells, which are considered to be motor cells involved in a local positive feedback loop to provide enhancement of the travelling wave in the basilar membrane.  

The kinetics of acoustic transduction are not fully determined; however, the processes are likely to occur on a microsecond time scale. In 1983, Hudspeth’s school proposed the tip–link model. Tip-links connect adjacent stereocilia to form mechanical linkages that open and close the transduction channels. When the hair bundle is deflected towards the tallest stereocilium, the cation-selective channels open near the tips of the stereocilia, allowing K⁺ inflow into the hair cell down the electrochemical gradient. The resulting depolarization of the hair cell opens the voltage-gated Ca²⁺ channels in the cell soma, allowing the entry of Ca²⁺ and the release of a neurotransmitter onto the nerve ending of the auditory nerve. When a depolarizing (positive) current was injected, an isolated hair cell showed voltage oscillation responses. What is the problem in this tip-link model of the mecano-electrical transduction of sound waves? According to the tip-link model, the K⁺ entry through the K⁺ channel at the top of the hair cell causes inflow along the electro chemical gradient. This model is unlikely because many actin filaments in the ciliary cells are packed densely in the hair cell, especially in the bottle neck part at the base of the hair bundle where the density of the actin filament are quite high, as described in the textbook. Therefore it can be assumed that all the water molecules in the hair cell assume bound water, not bulk water, because of the narrow diameter with a long length (0.1 μm × 2–3 μm), which largely reduces the K⁺ diffusion speed. But the hair cell vibrational frequency must be corresponding to 20 KHz, which means K⁺ concentration changes in the soma must also follow such a high frequency. It is almost impossible to control K⁺ concentration change from far away hair tip channel within 5 micro-second (corresponding to 20 KHz). This tip-link model cannot explain the ototoxic effect of neomycin, which has 22 positive charges per molecule. The toxic effect of neomycin was explained as a blocker of the Ca²⁺-activated K⁺ channel or Kᵢ channel. A more attractive and/or plausible model should be considered if PIP₂ is involved in the sound transduction, as explained below.

B. Electret microphone model

The surface of a hair cell is exposed to endolymph which is rich in K⁺ (about 160 mM) with a low Na⁺ (less than 1 mM) which is made stria vascularis cochlea. Furthermore PIP₂, which is usually localized in the internal surface of the plasma membrane, was found to be outer surface of the hair cell membrane. The direct evidence of PIP₂ localization on the hair cell membrane was shown in research on the cochlea of guinea pigs using the PIP₂ antibody. The application of neomycin to hair cells caused the suppression of mechanosensitivity, generating microphonic-potential directly recorded by microelectrode near the cochlea, in which electric response of the cochlea hair cells to acoustic stimulation is generated. In this case, one PIP₂ molecule has four negative charges when it is exposed to the saccular media. If a negatively charged membrane vibrates with the vibrating pressure from the tectorial membrane, the hair cell will generate a membrane potential change, according to the principle of the “Electret condenser microphone”, which directly activates the voltage-dependent Ca²⁺ channels. This model can explain neomycin toxicity without any contradiction; a single neomycin molecule can neutralize more than five PIP₂ molecules. These suppressive effects of neomycin were neutralized by application of excessive positive Ca²⁺. This finding verifies the assumption of competitive occupation at identical sites on the membrane by neomycin, and the assumption was proved by the NMR experiment.

Spectroscopic transduction mechanism for olfactory reception

A. Transduction of olfactory signals

Once an odorant molecule is bound to an odor receptor protein, whose gene family was discovered by Back and Axel (2004 Nobel Prize awardees), a receptor potential was
generated in the olfactory epithelium that is interpreted by the brain. Odorants in the mucus bind directly to one odorant receptor molecule located in the membrane of cilia. This association activates an odorant specific G-protein and adenylate cyclase, resulting in the generation of cAMP as a second messenger, which activates the cAMP-gated cation channel, resulting in depolarization. The receptor potential is reduced when cAMP is broken down by specific phosphodiesterases (PDE). Simultaneously, Ca$^{2+}$ activated calmodulin binds to the channel and reduces its affinity for cAMP. The entered Ca$^{2+}$ is excluded through the Ca$^{2+}$/Na$^+$ exchange pathway. This model appears very likely; however, there is a very serious, unnoticed problem to be resolved: How do the receptor proteins recognize different odorants, by shape or by molecular vibration frequency?

**B. How receptor protein recognize odorant molecule?**

The majority of recent research has accepted that receptor proteins recognize the shape of odorant molecules; however, there is much conflicting evidence concerning this structure–odor relation model. Molecules of widely different structure can have similar odors, e.g., the bitter almond character is shared by 75 molecules; however, it involves a triatomic molecule, HCN. Minor changes in the structure of a molecule can completely alter its smell character. The strongest test for the structure-odor relation model is the replacement of the hydrogen atom (mass 1.007) with the deuteron (mass 2.014) of the odorant molecule, which is called the isotope effect. When the proton of the odorant molecule is replaced by the deuteron, the smell will be completely changed without shape changes. Many deuterated molecules are commercially available, and the most striking results were obtained by using acetophenone and d-type acetophenone; d-type acetophenone is fruitier with a less toluene-like character than acetophenone and a much stronger bitter almond character. These results encourage researchers who accept the molecular vibration theory initially proposed by Dyson and modified by Wright et al.

**C. Molecular vibration model of odorant reception**

This theory originated from the simple question of why very different structures have similar odors. To understand the experimental results, Dyson suggested that the olfactory organ might detect molecular vibrations. If the entire vibrational range to 4000/cm were detected by a Raman or IR spectroscope, the detection of functional groups would be possible a biological spectroscope named “inelastic electron tunneling spectroscopy” (IETS), which relies on the interaction between electrons tunneling across a narrow gap between metallic electrodes and the molecules in the gap. According to the explanation of IETS by Turin, when the receptor protein accepts electrons from a soluble electron donor, the electrons are unable to tunnel across the binding site if the receptor binding site is empty; whereas if an odorant occupies the binding site, the electron can lose its energy during tunneling by exiting its vibrational mode and reduce the disulfide bridge via Zn$^{2+}$ located in the receptor protein, exciting its vibrational mode. Electrons then flow through the protein and reduce the –S-S- bridge via Zn$^{2+}$, thus releasing the G-protein for the further transduction step. This theory is based on the oxidation—reduction theory of the disulfide bond with the aid of Zn$^{2+}$.

**D. Novel proton signaling model of odorant reception**

An alternative model is available using the identical receptor protein except for the bound water on the receptor protein proposed by Mentre. Water molecules have electric dipoles. On contact with macromolecules, these dipoles arrange themselves in a non-random, very constrained manner, completely reflecting the patchwork of the macromolecule surface domain regardless of whether it is hydrophobic or hydrophilic. Water molecules bound to consecutive polar amino acids (Asn, Cys, Gln, Ser, Thr, Tyr) in a polypeptide chain, they can bind, forming H-bonded lines. Hydrogen bonded lines can be formed along the apolar surfaces in clathrate-like structures. These water molecule lines are good conductors of protons. Consequently, cell water (not only inside but also outside) is strongly constrained by the macromolecule surface. The thickness of this water layer was estimated as 0.3 nm. Because odorant cilia is in mucosa, odor molecules in the air are initially dissolved in the mucosa and form a microcrystal, as was proposed by Pauling. In this case, only specific molecular vibration signal of odorant molecule, not molecular shape signal, can be transferred to bound water layer with high impedance on the receptor protein. After the activation of vibrational signals to bound water layer can be reached to the receptor protein with specific vibration signals. In this step, different vibrational frequencies differentially activate the receptor protein, which activates the G-protein as shown in Figure 4. In this case, vibration energy might be converted to a proton current associated with cAMP production by an unknown mechanism.

**Perspectives**

It is generally accepted that the bound water in the ciliary cell changes three types of sensory transduction mechanisms. The reason that the role of bound water in signal transduction has not been considered might be because the physical chemistry and/or biophysics have been neglected.
and a cyclic nucleotide will control Ca\(^{2+}\) phosphorylation process.

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In the signal transduction process, the diffusion of the 2\(^{nd}\) messenger in a cell was considered to be a rate-determining process. According to the novel theory of cell water, there is no free water inside the cell, and, accordingly, all the molecules in the cell can move only by a carrier or by association with a proton current. The elongated shape of the ciliary cells has the disadvantage of ionic diffusion. If that is the case, Ca\(^{2+}\) is a strong candidate for being a 2\(^{nd}\) messenger, and a cyclic nucleotide will control Ca\(^{2+}\) signaling via the phosphorylation process.

This article is the expanded work of a former review\(^5\).

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