

# Sound-Sensitive Molecules

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## Introduction

Humanity has been wondering about the mechanisms of hearing for over 2,000 years. Many theories have been developed trying to solve this problem. The organ of hearing is still the only sense organ that is not fully understood. There is no doubt that the truth about hearing is different from the one proclaimed by the orthodox theory of hearing under the name of Bekesy's traveling wave. In order to change the seemingly erroneous status quo in explaining the mechanisms of hearing, I propose to start an analysis of all the circumstances that appeared after the announcement of the traveling wave theory. A new picture of hearing is emerging, significantly different from that described in textbooks and numerous publications. Censorship by orthodox reviewers can no longer inhibit new knowledge about hearing. This paper indicates the gaps in the current hearing theory and presents a new philosophy of hearing.

**Keywords:** Sound Wave; Basilar Membrane; Natural Vibrations; Resonance

**Abbreviations:** Pa-Pascal; pm-picometer; ms-millisecond; OHC-outer hair cell; IHC-inner hair cell; EAC-external auditory canal; ATP-adenosine triphosphate; cAMP-cyclic adenosine monophosphate; cGMP-cyclic guanosine monophosphate; DAG-diacylglycerol; IP3-inose triphosphate

## Analyzes and Facts

1. The hearing threshold of a young person at 1000 Hz is 0 dB, i.e. the sound wave pressure is  $2 \times 10^{-5}$  Pa. Converted to wave amplitude =  $8 \times 10^{-12}$  m, or 8 pm [1]. The amplitude of the sound wave that a barn owl hears is 1 pm [2]. If the average size of the atoms constituting the basilar membrane is  $10^{-10}$  m, the formation of a traveling wave at such an amplitude of the sound wave is doubtful. Such signal reaches the receptor. This indicates a different signal pathway to the receptor, not related to the basilar membrane.
2. Cochlear implant surgery in the case of partial deafness immobilizes the basilar membrane by introducing electrodes into the tympanic duct [3]. The lack of wave traveling on the basilar membrane does not result in hearing loss as before the surgery.
3. The basis of the traveling wave theory is the resonance of a longitudinal sound wave in the fluid of the atrial duct with a transverse wave of the basilar membrane (4). It is difficult to explain the resonances of a 100 Hz wave with a length of 1450 cm in the fluid with a transverse wave of the basilar membrane whose length = 3.2 cm. The natural vibrations of the human basilar membrane were incorrectly assumed to be in the range of 16 Hz–20 kHz. The basilar membrane is loaded with the organ of Corti. These vibrations take place in the fluids of the cochlea, which have significant damping properties. The traveling wave for low tones cannot grow from the oval window to the cap because there is no resonant capacity in the initial section. Studies of human tissues have shown that the natural vibrations of various tissues range from 8 to 100 Hz [12]. The hearing mechanism of small mammals and birds is the same, they have basilar membranes from 2 to 5 mm. They hear sounds from 5 Hz (pigeon) to 200 kHz (bat). Moths do not have a basilar membrane or ear fluids and can hear up to 300 kHz. This points to the existence of different hearing mechanism.
4. Quiet tones are amplified by 40 dB [5]. Why do we still hear them as quiet when they are amplified 10,000 times? Quiet tones below the auditory threshold cannot be amplified using this method because they do not cause OHC depolarization. The amplification is supposed to consist in the pulling of the basilar membrane by contracting OHCs during depolarization. The difficulty of this mechanism lies in the amplification of polytones of different frequencies, having aliquots and phase shifts. Amplification of quiet sounds using this method separates the transmitted information. Loud tones are received and transmitted to the brain. Soft tones require time-consuming amplification. At this time, there is another traveling wave on the basilar membrane and pulling the basilar membrane disrupts its run. Amplification of quiet sounds whose energy is too low to reach the brain are amplified molecularly in the hearing cell.
5. Directional hearing: Humans have an interaural distance of approximately 20 cm, which makes the time difference of the signal reaching the brain from different directions equal to 0.0572 ms due to the path difference. A barn owl with an interaural distance of approximately 5 cm perceives a time difference of 0.0143 ms. It receives sounds 20 dB below our hearing threshold, with a wave amplitude of 0.001 nm. According to the traveling wave theory, these waves should be mechanically amplified. The difference in the intensity of the wave heading to both ears is also recognized, caused by the loss of energy along the way [2].
6. Inertia: Elements of the middle and inner ear that have mass are set to vibrate. There is acceleration in wave motion. The inertia in this wave motion is:  $(2 \pi \times \text{frequency})^2 \times \text{amplitude}$ . In Bekesy's theory, inertia is not properly taken into account. In wave motion, inertia increases proportionally to the square of the frequency of the vibrating mass [6]. It is important for high frequencies. A sound wave has no mass and is not subject to the law of inertia. It goes to the receptor through a different route.
7. Frequency resolution: The traveling wave theory relates the ability to recognize frequencies to resonance with the basilar membrane. When the basilar membrane is immobilized, wave resonance is also disabled and frequency resolution is preserved. The ability of the hair cell receptor to receive a specific stimulus in the form of a sound wave with a limited frequency determines frequency discrimination. The hair cell receptors are molecules sensitive to the mechanical energy of the sound wave (sound-sensitive molecules), responsible for gating the potassium mechanosensitive channels of the hair cell wall.

8. Energy quantization: The sound wave transmits quantized energy to the receptor, which means that the increases and decreases in energy are sudden. There is no continuity of changes at every stage of information transmission [7]. In Bekesy's theory, the adoption of this principle is impossible in relation to fluid flows, pulling up the basilar membrane by OHC contractions, tilting or bending hairs of hair cells, or tensioning cadherin threads connecting adjacent hairs (tip-links mechanism). Cadherin threads cannot close potassium channels. It was figured out (J. Hudspeth) that this task is performed by myosins. For high frequencies, myosins are too slow.

9. Energy transformations on the way to the receptor. Longitudinal wave in the atrial fluid - transverse wave on the basilar membrane - longitudinal wave of the cochlear fluid mass - tilting of the hairs of the hair cells - tightening of the cadherin threads - opening of OHC potassium channels - depolarization of the OHC - contraction of the OHC - pulling up of the basilar membrane (at this time there are already other waves on the basilar membrane) - amplification of the wave deflection (which) - increased movement of cochlear fluids - tilting of IHC hairs - reception and transmission to the brain [8]. Two questions arise: Why does the enhanced fluid movement in the subsegmental space only cause the IHC hairs to tilt and not the OHC hairs at the same time? The second question concerns OHCs - they have afferent innervation, but they do not send information to the brain, because according to the theory, they only serve as an amplifier for IHC.

10. Polytone encoding: There is no explanation of how information about polytones with numerous harmonic components and phase shifts is encoded by the basilar membrane, cochlear fluids, hairs of hair cells and cadherin filaments.

11. Oscillating (rocking) movements of the stirrup: The spherical incudostapedial joint allows the stapes plate to move in various planes. At low frequencies, it is a piston movement - used in stapedotomy operations. At higher frequencies, the stapes plate vibrates in the transverse axis of the plate. At the highest frequencies, the plate vibrates in the longitudinal axis of the plate. It should be noted that such plate movements cause one half of the plate to generate fluid movement towards the cap. Whereas the other half of the plate simultaneously generates fluid movement in the opposite direction [9]. Opposite fluid motion cannot encode and transmit information? How is resonance and traveling waves created on the basilar membrane?

12. OHC depolarization and contraction: According to the traveling wave theory, depolarization and contraction of the OHC affects the entire cell simultaneously. High sound intensities, causing depolarization, also induce OHC contraction [10]. What mechanism evaluates and protects against amplification of a loud signal? OHC contraction depends on cell depolarization, which depends on the operation of ion channels in the hair cell wall. In the operation of ion channels, absolute refraction occurs when the ion channel is insensitive to stimulus for approximately 0.1 ms. During relative refraction, only a large stimulus can activate ion channel. The channel inactivation time makes it impossible to depolarize the entire cell simultaneously more than 1000 times/s. There is a possibility of limited depolarization of a part of the cell membrane, but then the pulling of the basilar membrane by OHC is impossible. The outer hair cell does not have direct communication with the basilar membrane, so the transmission of quantized energy through this route is questionable. Experimental studies have shown that a hair cell can contract up to 50,000/s. The error of the experiment is that the cell wall was irritated with electric current, causing depolarization. And the frequency of contractions of the entire cell is limited by the refraction of ion channels blocking OHC contractions to 200 kHz.

13. Resonance of the longitudinal wave with the transverse wave of the basilar membrane. Research has shown that a sound signal lasting tenths of a ms is received by the receptor [11]. One or even 2 periods of the forcing wave are not able to convey full information to the forced wave. A 100 Hz wave with a wavelength of 14,500 mm in fluids is not able to force resonance on a 32 mm long basilar membrane in humans or a few millimeters in other well-hearing creatures.

14. Signal travel time: Electrophysiological studies show that the signal travel time from the EAC to the auditory nerve is 1.5-1.9 ms. However, the signal travel time through the basilar membrane and cochlear fluids is 5-6 ms, and for quiet, amplified tones it would be much longer.

15. False assumptions were made for the calculations:

a) According to the theory, the basilar membrane is an independent entity - a thin string vibrating in the air. The organ of Corti load and fluid attenuation were not taken into account [12].

b) It was assumed for the calculations that the cochlea is a straight pipe narrowed in half of its length. This changes the anatomy and physiology of the inner ear.

c) It was assumed that the wave travels on both sides of the basilar membrane, resulting in a wave traveling on the basilar membrane. To support this thesis, Bekesy removed Reissner's membrane from the ear and connected the atrial duct with the cochlear duct so that the sound wave ran along the basilar membrane. According to Bekesy's concept, a sound wave passes through Reissner's membrane, through the fluid of the cochlear duct, through the tectorial membrane, the fluid of the subsegmental space and through the organ of Corti with auditory receptors to reach the basilar membrane to cause a traveling wave. The energy of the sound wave passes through the hearing receptor and the information is not received by the receptor? Because for this concept, a wave traveling on the basilar membrane must be created.

## Conclusions

Taking into account the circumstances mentioned above, a new picture of our hearing appears, described for almost 20 years under the name "Submolecular theory of hearing" [13]. The fundamental novelty of this theory is the change in the signal path to the receptor. The information received by the eardrum is transmitted to the bone casing of the cochlea through the eardrum itself, the ossicles of the middle ear and especially the stirrup plate. The wave travels through the cochlear bone casing at a speed of about 4000 m/s straight to the receptor. The mechanical energy of the sound wave is received by hair cell receptors, which are capable of receiving a very narrow frequency band. Each neuron connected to receptor has a limited receptive field, capable of receiving a signal of a limited frequency. At the neuron I level, there is the possibility of temporal and spatial summation and collateral inhibition. The quantized sound wave energy encoding information is received without changing the information content by specialized sound-sensitive molecules. The energy of sound wave is wave energy, so the transmission mechanism may be based on the resonance of waves transmitted with elements of molecules sensitive to a given frequency. The energy received by molecules causes various changes in them. The number of possible changes is proportional to the square of the number of atoms that make up the molecule. For example, for a molecule consisting of 20 atoms, the number of possible changes is 1020.

A molecule is a collection of atoms connected by bonds of various lengths. They have different mass and different numbers of protons and electrons. Atoms vibrate at different frequencies. Electrons in orbits give rise to electronic energy, electrostatic energy. Dipoles are formed due to atomic bonds. In addition to the translational motion of atomic nuclei, there is also rotational motion. Atomic bonds create angles between bonds - valence and rotational. Each bond, each oscillation, has its own energy, which, when added up in the molecule, gives the molecule's own energy. Each atomic bond of elements has a specific frequency of natural vibrations. There are 3-4 times more bonds than atoms in molecule. The number of such atomic bonds in 1 mm<sup>3</sup> molecule has been calculated, and there may be about 10<sup>18</sup> of them. Each atom with  $n$  electrons has a specific energy. Valence angles and rotational angles influence (their change) the change in total energy. There are isolated molecule vibrations, stretching vibrations, bending vibrations, and intermolecular vibrations. According to the law of Nature, molecule searches for the bottom of the well, i.e. the lowest possible total energy [7]. It has the ability to emit energy in the form of photons in order to absorb the lowest possible energy at a given temperature. A molecule that has received energy from a sound wave (sound-sensitive molecule), has increased total energy, tries to return to the basic energy, transferring the obtained energy to an adjacent molecule through photon radiation, through oscillations, vibrations or through its own conformational changes acting through contact on the adjacent molecule. This molecule, by obtaining quantized energy originally derived from the sound wave, creates a new conformer, capable, thanks to the energy received, of regulating the mechanism responsible for gating the potassium mechanosensitive channels of the hair cell wall.

The rate of energy absorption and transfer by molecule is approximately 1015/ s. Through the open potassium channel, 6000 K<sup>+</sup> ions/ms pass from the endolymph into the cell, starting the cell's depolarization. At the electronic, atomic and molecular level, the information contained in the sound wave is transferred to the hair cell. The work of the hair cell with the mechanism of intracellular amplification, producing a transmitter, was discussed in the paper "Submolecular theory of hearing"[9]. Intracellular amplification is a whole complex of molecular factors such as: phosphorylation and dephosphorylation of ion channels responsible for the conductivity of cell membranes, ATP concentration, cAMP and cGMP levels, cell's pH, osmotic pressure, and the presence of ligands. It is related to the regulation of calcium levels in the cell, with the work of proteins binding to calcium, where calmodulin plays an important role, influencing the production and breakdown of cAMP and cGMP. It activates protein kinases and phosphatases and regulates the functioning of the calcium pump. It affects the contraction of muscle and non-muscle cells by activating the cAMP-independent myosin light chain kinase. Calmodulin affects exocytosis. Saturation of the 4 domains of calmodulin increases its effect up to 10,000 times. Calmodulin, together with calcium that changes level during stimulation, affects metabolic processes in the cell by affecting the so-called key enzymes. The interaction of all cell organelles is regulated. The process of enzyme production or the rate of their degradation is regulated. Calcium is the second transmitter of information in cell, acting faster than the other second transmitters: cAMP, cGMP, DAG, IP<sub>3</sub>, which are produced in connection with an increase in calcium levels or activated by G-protein. The stage of generation of second transmitters is one of several mechanisms of intracellular amplification. One enzyme molecule can produce several hundred second transmitters [13].

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