

Submolecular Theory of Hearing

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ABSTRACT

Today's travelling wave theory is lacking in elucidation of hearing and recognizing of frequencies of sounds whose duration times are shorter than decimal parts of milliseconds. Attention was paid to the problems of encoding information on the way towards a receptor as well as to the time of signal latency on the way to the centre. Addressed was the issue of inertia in the middle ear and the inner ear, concerning mainly high frequencies as well the intracellular amplification. Presented were new hypotheses of hearing mechanisms regarding our power of hearing or listening. A new theory of hearing has been referred to as Submolecular theory of hearing. This new theory concerns a change in the pathway of the signal to a receptor. Vibrations travel through to the bony housing of the cochlea and through an osseous tract information is conveyed to a receptor. This can be corroborated by the latency times of the sounds under examination, even shorter than decimal parts of millisecond. The second hypothesis concerns the mechanism with which the sound wave energy is converted to the receptor potential of the acoustic cells. I postulate that this does not occur through the basilar membrane and cochlear fluids. Mechanical energy of a sound wave acts upon protein molecules (sound sensitive molecules) responsible for generating the motion of the gating mechanism of opening of K⁺ mechanosensitive ion channels. The energy of a sound wave acts upon ionic and covalent bonds, changes the angles of bonds as well as vibrations of particles and atoms. It also changes the activity of enzymes. Conformational changes of proteins may support the gating mechanisms. Proteins will be stretched and rolled up, which gives rise to a motion of molecules. Information transferred by a sound wave may be precisely conveyed. The third hypothesis concerns signal amplification. According to a new theory, there exists an intracellular amplification on a molecular level. New vibrometric examinations on the conduction of soft tissues and bones in the cochlear housing in conjunction with chronometric analyses of the times constituting the reception and processing of auditory information will corroborate the hypothesis. This will allow improving the results of medical procedure – viz. stapedotomy as well as of pharmacotherapy. In the case of stapedotomy, the question is to guarantee also an improvement in hearing high frequencies, which is feasible when acknowledged, is a pathway of a signal to a receptor, different from today's pathway.

Keywords: Middle ear; Amplification; Receptor; Acoustic cells; Intracellular amplification; Protein molecules = sound sensitive molecules; Stapedotomy

Introduction

The prevailing theory of hearing, elaborated and pronounced in the first half of the 20th century does not explain - according to the state-of-the-art - all mechanisms governing the reception, processing and conveying of auditory information [1]. Numerous papers are still merely a continuance of Bekesy's travelling wave theory, based upon the hydrodynamics of cochlear fluids. A sound wave directed to the atrium of meatus generates a transverse wave travelling upon the lamina basilaris which at its maximum displacement reduces the distance between the lamina basilaris and the tectorial membrane, which triggers an endolymph flow and bending of the acoustic cell hairs [2]. Those hairs are connected one with another with tiny cadherin fibres which become tensioned, triggering the K⁺ gating mechanism of mechanosensitive channels upon the hairs of acoustic cells. For the closing of those channels responsible are to be molecular motors in the form of myosins, moving along actin filaments. The route of a signal to a receptor is time-and-energy-consuming. The wave amplitude in the cochlear spiral-shaped duct will disappear very rapidly. It was accepted that contractions of external acoustic cells are able to amplify the wave travelling due to a contraction of a cell after a stimulation and depolarisation [3]. In compliance with the travelling wave, quiet sounds are amplified by 40-50 dB. Sounds above the auditory threshold are amplified 10,000 times, but we still hear them as quiet sounds. In the case of sounds composed of loud and quiet tones, the loud ones are perceived, and information is sent to the centre. Instead, quiet sounds which need to be amplified with this method are separated and directed to the amplification route by an OHC's contraction and lamina basilaris rolling up so as to amplify the wave travelling in that time. That amplified wave generates more intensive endolymph movements and causes IHC hair to bend more. Such a piece of information of quiet sounds may be conveyed to the centre independently from loud tones and that with a big delay. Such an information splitting and delay in the message is unacceptable. According to this theory, the lamina basilaris is responsible for the frequency resolution through sound wave resonance with an appropriate lamina basilaris position thanks to its anatomical structure. Information has to be transmitted very rapidly and with high precision, which is decisive for the life of many animals or even for the survival of species. This is impossible with such a long signal pathway to a receptor, especially in the case of quiet sounds, mechanically amplified and most important. Then, there are also problems with information encoding through flowing fluids, bending acoustic cell hairs and tensing cadherin fibres. The key items are the harmonics and phase shifts, indispensable for the recognition of timbres.

Hypothesis

In some aspects, the new hypothesis - Submolecular theory of hearing - differs fundamentally from Bekesy's travelling wave theory. The main difference consists in postulating a different signal pathway to a receptor. After amplification, a signal in the middle ear is conveyed to the bony housing of the cochlea, where it reaches the receptor at a speed of 4,000 m/s. The signal is simultaneously conveyed to the cochlear fluids. Hence ascertained is a wave travelling on the lamina basilaris and pressure difference on both its sides [4]. Basing upon the research into the behaviour of a sound wave on the way from the middle ear to the oval window in the rolled up cochlea, it should be concluded that the energy proceeding towards the oval window is not the energy heading in a channel for a receptor. It was proved that the amplitude of that 90 dB and 8000 Hz wave diminishes between the external auditory meatus and the oval window from 500 nm to 0.5 nm, viz. 1,000 times. Since the wave energy is proportional to the square of the amplitude, the energy of this wave is reduced by one million times [5, 6]. It should be deemed that this is the so-called degraded energy. This energy - disappearing in the cochlea and travelling from the oval window to the cupula and further on to the oval window - will not proceed towards the receptor and cannot be held responsible for conveying information. Apart from that pathway, at such a giant energy loss through the cochlear fluids and the lamina basilaris, there must be another transmission channel for a signal to the receptor, through a bone, without such losses. The signal, viz. useful energy, reaches a receptor of acoustic cells provided with a specific sensitivity to a given length of sound wave. Those cells are arranged along the lamina basilaris and in compliance with the tonotopy principle information is conveyed to the centre. The acoustic cells arranged in the initial section of the lamina basilaris can perceive high frequencies. While approaching the cupula, lower and lower frequencies are perceived. The location where frequencies are received is conveyed to the central nervous system with high precision. Basing thereupon, the frequencies are subject to evaluation and analysis. A significant role is played by the size and the location of receptor fields from which pulses in the form of stimulating potential reach a nervous cell in the spiral ganglion. The transmission of information to the receptor must comply with the sound wave at the entrance to the system. A conversion of encoded energy of a sound wave into receptor potential occurs on a level of molecular transformations. In an acoustic cell, a mechanical signal of a sound wave generates receptor potential, which leads to a transformation of energy into a form of chemical bonds of transmitters of intracellular information. Perceived are

sounds above the sensitivity threshold. Quiet sounds whose energy is too small for reaching the centre are subject to an intracellular amplification on the molecular level. The energy of the signal conveyed by the auditory nerve is amplified due to depolarisation in each node of Ranvier. The intracellular amplification is controlled and it regards the signals received. The transmitters – produced and allocated for a synapsis - trigger a conversion of chemical energy of transmitters of intracellular information into electrical energy and generates post-synaptic stimulating potential which in the nervous cell of the spiral ganglion is transformed into action potential, conveyed by myelinated auditory nerves to the CNS [central nervous system]. A certain role is played by spatial and temporal summation as well as post-synaptic inhibition. Adaptation plays an important role at high intensities.

Justification of the hypothesis

Numerous observations presented below speak against today's prevailing theory of travelling wave, and simultaneously they speak in favour of the submolecular theory of hearing.

Mechanism of threshold hearing

Humans can hear a sound of 1000 Hz with pressure amplitude of approx. 2.0×10^{-5} Pa. Wave intensity is proportional to the square of its amplitude and pressure. By conversion of the pressure amplitude into the wave displacement, we obtain a quantity of 8×10^{-12} m = 8 pm. This quantity is far and away smaller than the diameter of atoms of the elements constituting the structure of the lamina basilaris (viz. atom diameters: hydrogen – 50 pm, oxygen – 120 pm, phosphorus – 190 pm, iron – 240 pm, copper – 256 pm, sodium – 360 pm, potassium 400 pm). The amplitude of the threshold wave is 8 pm, viz. the sound wave in the external auditory meatus. Neglecting the impedance and amplification of the middle ear wave, the amplitude of that wave conveyed to the atrial fluid is smaller than the one in the external acoustic meatus, among other things, because the lever mechanism of the middle ear decreases the wave amplitude at a ratio 1.3:1. A decreased wave in the cochlear fluid has to cause – according to the travelling wave theory – a pressure difference on both the sides of the lamina basilaris, which as Bekesy has it, is the source of a wave travelling on the lamina basilaris. According to this theory, quiet sounds are amplified by 40 dB. Here is a contradiction since the signal amplification depends upon a receptor's stimulation and OHC's contraction [7]; therefore, tones quieter than the threshold tone cannot be amplified. Upon a receptor's stimulation and OHC's contraction the lamina basilaris should be rolled up at a specified place on the lamina basilaris, depending upon the frequency, there should occur an increase in the cochlear fluid flows, bending of acoustic cell hairs, and eventually, IHC's stimulation. The travelling wave theory does not explain how such small wave amplitude close to the auditory threshold, disappearing, can generate a pressure difference on both the sides of the lamina basilaris. If there is no pressure difference, there will be neither a traveling wave nor amplification. According to the travelling wave theory, sounds amplified by 40-50 dB are still heard by us as quiet sounds. The threshold stimulus has to trigger a receptor potential. A smaller intensity of a stimulus, even specific, is not perceived as an auditory sensation and cannot be amplified mechanically through an OHC's contraction. We do not perceive energy under the auditory threshold – it is not a stimulus for us. A quiet, received signal is amplified intracellularly.

Cochlear implant vs. signal path towards a receptor

Another problem resulting from the travelling wave theory appeared with the implementation of cochlear implant surgery in case of partial deafness. Here is applied Johansen – Müller's law of specific nerve energies: an irritation of any spots on the sensory tract (neuron or axon) triggers psychical sensations such as if the receptor itself were irritated. In the procedures performed, 20 electrodes are introduced into the ear canal through the oval window. Electrodes are up to 25 mm long and immobilise entirely the lamina basilaris. Obtained is an improvement in hearing in the almost deaf part, without deterioration of hearing which was earlier in the part with better hearing, despite exclusion of the lamina basilaris. This implies that the signal pathway to the receptor is not connected with the lamina basilaris. A wave travelling on the lamina basilaris cannot be of any importance for the sense of hearing. The signal must proceed to the receptor via another pathway.

Stapedotomy

Surgical treatment of conductive deafness speaks against Bekesy's theory. Stapedotomy is performed mainly in case of otosclerosis or otospongiosis with immobilisation of the stapes plate in the oval window. A hole is made in the stapes plate; then, a small piston connected with the long limb of the incus and passing through the hole in the stapes plate conveys vibrations to the fluid in the vestibular canal. According to the prevailing theory, there should be an improvement in hearing for all frequencies. In most cases obtained is an improvement in frequencies of up to 2 kHz, sometimes to 4 kHz, and seldom to 6 kHz. A surgical procedure in line with the prevailing theory, performed perfectly, does not deliver the expected result, since the signal is sent exclusively to the cochlear fluid. A young, healthy man can hear sounds of up to 20 kHz. The same young man, after performing the procedure, can hear only sounds of 2 kHz - 6 kHz. This shows high frequencies are not conveyed to the receptor this way. According to my hypothesis there must exist another way, not via cochlear fluids.

Signal's travelling time to the centre

Electrophysiological examinations – ECoG, ABR and BERA - proved that the time required by the signal to travel from the external auditory meatus to the trunk of the auditory nerve amounts to 1,5 – 1,9 ms. Instead, according to Bekesy, the summing up of time spans of all sections of the signal pathway gives a total time 2-3 longer. If mechanical amplification via OHC contraction is taken into consideration, this time will be even longer. Bekesy performed some combinations inconsistent with the anatomy and physiology to justify the correctness of his own theory. He straightened the cochlea to a straight tube and after such a conversion he performed calculations for the cochlea. If the cochlea is straightened, its physiology will be fundamentally altered. In addition, as he wanted to obtain a wave travelling on both sides of the lamina basilaris, he connected the atrium meatus, removing Reissner's membrane from his calculations. This is inconsistent with the physiology because those ducts have different compositions of electrolytes; moreover, the cochlear duct has a blind end and no connection with the eardrum meatus. A connection made between those ducts means that the mechanical energy of the sound wave falls through the tectorial membrane directly upon the receptor of acoustic cells in the joint duct. The energy of a sound wave is a stimulus adequate for the auditory receptor. It is rather unlikely to deem that the auditory receptor does not respond to a specific stimulus, whereas it reacts to the pulling at cadherin fibres. Bekesy also wrongly assumed the quantity of natural frequency of the membrane basilaris from 16 Hz to 20 000 Hz. Small mammals have very short lamina basilaris (2-3 mm), but they can perceive sounds of up to 200 kHz. Therefore, the frequency resolution cannot depend upon the membrane basilaris and resonance. Bekesy neglected an important fact that on the inferior surface of the membrane basilaris there is a thick layer of connective tissue, whereas the mass of the organ of Corti is located on the superior surface. The whole complex is immersed in fluid exhibiting strongly suppressing properties. In the electrophysiological tests, the latency time – from the signal in the external auditory meatus until the occurrence of receptor potential (microphonic potential) – was determined as 0 (zero) ms. With more accurate measurements, this time amounts to 0.005 ms. Such a short time would be impossible to achieve in case of bypassing through cochlear fluids and the lamina basilaris – where a wave travels on the membrane at an average speed of 50 m/s, of bending acoustic cell hairs, pulling of cadherin fibres at the mechanism gating the K⁺- mechanosensitive channel while amplifying mechanically quiet sounds, the actual time is yet longer. This is another premise that a signal must proceed towards the receptor via bone [8]. By using Gaussian pulses with duration times under decimal parts of seconds, there was ascertained a dependence between the recognition of frequency and the signal's duration time. The discrimination threshold for the duration time of a pulse depends upon the pitch and duration time. Those investigations again exclude the occurrence of resonance. They prove that at such short signals it is possible to recognize the wave frequency of a signal whose duration time is even shorter than one wave period. Such a signal cannot reach the receptor in a roundabout way. A very important auditory mechanism concerns the transmission of information comprised in a sound wave to the receptor. The procedures related to this mechanism, according to the travelling wave theory referred to as tip-links – raise a lot of doubts. It was assumed that the bending of acoustic cell hairs tensions up cadherin fibres which pull at the gating mechanism of the K⁺ mechanosensitive channels on the acoustic cell hairs [9]. There is lack of clarity how cadherin can open ion channels at a frequency of up to 20,000/s. in man and up to 200,000/s in a bat, it is inconsistent with the law of inertia. An open channel must be closed with precision. The diameter of the most important part of the passage section in the potassium channel is 0.3 nm. The gating mechanism of the channel is responsible for the movements of the opening and closing mechanisms within a range of 0 to 0.3 nm, in the case of 10 kHz and a time of 0.1 ms. In the prevailing theory of hearing it was assumed that myosins [10] are responsible for channel closing. It is impossible. The investigations showed that the contracting cycle – time of the cycle of myosin's movement upon the actin filament is too long and amounts to 15 ms. The

working step of that myosin is exceptionally long and amounts to 30-36 nm. Myosin VI performs several working steps, covering a distance of approx. 200 nm, and myosin becomes detached from the actin filament. In the course of such a march, it also performs sporadically a step backwards. Length of myosin 1c = 70 nm, double-headed myosin VI: 50-70 nm. Thickness of the myosin tail = 2 nm (2 heavy chains). The transport rate through non-conventional (non-muscular) myosins is approximate to the rate of kinesin and dynein. For those transporters, at a minimum load, the rate amounts to 0.6-2.3 $\mu\text{m/s}$ – and this is rapid transport. In most cases, this rate amounts to 0.012-0.12 $\mu\text{m/s}$. Instead, at a big load this is slow transport = 0.002-0.012 $\mu\text{m/s}$. By assuming that releasing the tension of cadherin fibres while changing the bending of hairs would be a very big load; thus, the slowest rate - viz. 2 nm/s - should be accepted as the rate of steps. At higher sound frequencies, e.g. 10 kHz, this mechanism is entirely inefficient. Please note that the speeds related to a sound wave depend upon the wave frequency and intensity, and are very variable. Then, there is also another important question. Myosin as a biological motor, supplied with ATP energy, moves upon the actin filament in one direction. Sometimes a step backwards or a downtime is taken, but withdrawal from closing each cycle of an ion channel is excluded. Myosin cannot function cyclically, e.g. 10,000 times/s or 100,000 times/s, an additional moment – at an excessive load myosin stops functioning and becomes immobilized. The working mechanism of other myosins is very similar. Thirty-five types of myosins are known. Unsolved remains the problem of connecting myosin and actin with protein inside the ion channel, responsible for the opening and closing of a channel according to the sound wave energy, independently of inertia of those elements which have a speed, acceleration and their own mass. The lamina basilaris, cochlear fluids and hairs of acoustic cells – according to the prevailing theory – are responsible for the wave motion and are subject to the law of inertia calculated according to the formula:

$$(2 \pi \times \text{frequency})^2 \times \text{amplitude} \times \text{mass g/mm/s}^2.$$

Signal amplification

A quiet, received signal, but having too low energy to reach the centre is amplified with both the molecular method and intracellularly [11]. This mechanism is accurate and controllable. The potassium level in endolymph is higher than in the acoustic cells. Negative charges of proteins and a deficit in positive ions in a cell, caused by the operation of sodium-potassium pumps, generate a high electrochemical potential on the lamina basilaris. As distinct from Bekesy's theory, in which ion channels are opened by pulling at the cadherin fibres, the new theory assumes that the control of both the activation gate and the inactivation gate depends directly on the sound wave energy. The channel gates consist of protein molecules. The quantity of potassium ions traveling towards an acoustic cell depends upon the energy encoded in a sound wave. Within a 1 ms time, up to 6000 K⁺ ions may pass to a cell causing its depolarisation. If the depolarisation should exceed the threshold of about 10 mV, the calcium and sodium channels on the side walls of an acoustic cell, depending upon tension, will be activated. The depolarisation will increase, calcium flows into the cell, which triggers the release of calcium accumulated in the endoplasmic reticulum, mitochondria and the nucleus. Calcium combines with calcium – dependent proteins e.g. calmodulin. Those proteins, after combining with calcium, will increase their activity many times. Calcium with cAMP, cGMP, IP₃ and DAG is a transmitter of intracellular information. Calcium influences the production, transport and output of a transmitter. Cell's depolarisation acts upon prestin, a protein responsible for OHC's contractions. An acoustic cell functions upon 2 levels – viz. constitutive level, responsible for normal functioning, like in the case of each cell, and level 2, controllable, related to the production, transport and output of a transmitter. Those levels operate in tandem. With calmodulin and other proteins dependent upon calcium, signal transmitters, calcium participates in an intracellular signal amplification. Amplification occurs when the receptor has received a signal. After each signal, the calcium level in a cell goes down to a minimum. active Calcium pumps, ion exchangers are active; within the cell calcium is conveyed to the endoplasmic reticulum, mitochondria and to the nucleus. The lower the calcium level in the cell before stimulation, the stronger the reaction of the cell to a new stimulation.

Implications arising from the acceptance of the hypotheses

Because of new hypotheses new vibrometric tests are intended in conjunction with investigations into reaction time to confirm the conveyance of auditory information through the cochlear bony housing to the receptor of the acoustic cells. In particular, this regards high frequencies and intensities where inertia plays a significant role in the middle ear and the internal ear for the elements of signal pathway having a speed, acceleration and mass. A sound wave does not have a mass or inertia, so high frequencies may be transmitted through a bone. The acceptance of a hypothesis will allow one to understand better the auditory mechanisms, and obtaining better therapeutic results in a stapedotomy by drawing attention to the conveyance of high frequencies in a way different

then until now, in which case they did not reach the receptor this way through fluids and the lamina basilaris. Recommended are new vibrometric tests on soft tissues and the cochlear bone housing with simultaneous determination of reaction time to confirm the pathway and the auditory mechanism, especially in the case of high frequencies and very small intensities which are audible. The disappearance of energy of a wave of quiet tones on the way to a receptor through cochlear fluids excludes exceeding the receptor's stimulation threshold, and thus, those tones cannot be subject to amplification by OHC's contractions. In a new hypothesis chronometry plays an important role. The knowledge of the reaction time – the signal pathway to a receptor and the factors influencing that speed is significant for evaluating whether the process occurs correctly or is disturbed. It can be stated not only what the signal pathway is, but also whether there are any disturbances related to time and signal intensity. This hypothesis draws attention to the importance of rocking (swinging) movements of the stapes in the reception of high frequencies, which may be utilized for improving the results of stapedotomy.

Evaluation of the hypothesis

Both electrophysiological investigations and experiments indicate irrefutably a considerable decrease in the energy of a wave in fluids in a spirally shaped cochlea. In addition, a long time of the signal path implies the existence of another path covered by the signal travelling to the receptor. The postulated hypothesis with proofs can clearly and logically present the changes in today's travelling wave theory. A possibility of a rapid and faultless conveyance of auditory information is confirmed by a halved number of transformations of sound wave energy on the way towards the receptor as described in the travelling wave theory.

Evaluation of Evidence

Evidence in support of the hypotheses, and actually of a new theory of hearing, has been collected based upon an analysis of papers published by university centres worldwide, as well as upon results of electrophysiological tests and research done at various academic centres [12]. Analysed were the results of a procedure – viz. stapedotomy, cochlear implants and tympanoplasty. Those hypotheses are very likely and it may be forecast that further observations and experiments will corroborate those hypotheses constituting a new theory of hearing. Those investigations include laser Doppler vibrometry, electrophysiological and chronometric tests.

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