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Quantum Theory of Smell

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Abstract

The sense of smell is one of the most important and oldest sensory organs in humans and other living beings. Philosophers have been involved in the sense of smell since ancient times. In recent years, several new theories of smell have emerged. American scientists Linda Buck and Richard Axel were awarded the Nobel Prize in 2004 for developing the coding of olfactory receptors and the analysis of the signal path to the center. The new quantum theory of smell is very different from previous theories. In detail, he tries to explain the reception and transmission of the quantized energy of the odorous particles to the center. It takes into account all the stages of the journey and the mechanisms of this transmission. It describes the transfer of odorant energy to the acceptor and receptor and further through the G protein to the transformation of intracellular energy. It draws attention to the mechanism of formation of receptor potential and action potential. It emphasizes the importance of intracellular regulatory mechanisms related to cell life and the simultaneous transfer of odorant energy to the center. It describes the role of calcium in the cell, signal amplification and encoding of olfactory information.

Keywords: olfaction receptor; depolarization; potentiation; G protein; smell; receptor; amplification

Introduction

A new vision of smell

The research of Linda Buck and Richard Axel [1,2] on olfactory receptors at the genetic level led scientists to the conclusion that a multigenic family of genes encoding olfactory receptors is responsible for the reception of olfactory information. In the human genome, 339 complete genes encoding receptor proteins have been identified [3, 4]. The successive stages of the olfactory pathway were also studied. The Nobel Commission optimistically stated that the problem of smell had already been definitively solved. There are many indications that the research awarded the Nobel Prize in 2004 did not solve all problems related to smell [5]. The new quantum theory of smell differs significantly from the previous theories in several points. The basis of the theory is reception and transmission quantized energy from the odorant to the brain centers in proportion, regardless of molecular transformations at the atomic and electronic level throughout the course of complex transformations. An adequate stimulus for the olfactory organ is an odor molecule, i.e., a molecule containing from one to 17 million. Atoms. Every molecule, as well as every atom in a molecule, is in constant motion. Length of atomic bonds of hydrogen = 0.74 Å. The largest molecule is 1 µm long and 10 nm in diameter. It contains 17 million atoms, its molecular weight = 200 million Daltons.

The length of atomic bonds is constantly lengthening and shortening due to the vibrations of normal atoms. Atoms reach their maximum swings at the same time. They perform constant oscillating and rotational vibrations and vibrations around their equilibrium positions. The vibration frequency is between 1013 Hz and 1014 Hz. The vibration period is on average 10-12. The oscillatory deflection of the vibrations is 10% of the binding length. For the hydrogen molecule H-2, it is about 0.1 Å. Each molecule has its own basic energy. The external energy (odorant signal) causes a change in the potential energy of the acceptor and receptor, rotational excitation, a change in bond length, a change in covalent and torsion angles, a change in the total energy of the molecule, and finally a change in the conformation of the acceptor molecule that transfers energy to the G protein.

The kinetic energy of the molecule is associated with motion. In addition to kinetic energy, a molecule has potential energy, which is made up of chemical bonds, and the forces of electrostatic attraction and electromagnetic interactions. The sum of these

energies forms the internal energy of the molecule body. The internal energy also depends on the temperature and the mass of the molecule. The supply of the external energy of the odorant to the acceptor molecule results in an increase in the internal energy of the acceptor [6]. Odor molecules (donors) have a positive or negative electric charge or are inert. Neutral molecules transfer energy through the energy of particle collisions and the merging of electron clouds of molecules. Each atom has electrons that form an electron cloud around the nucleus of the atom. The size of this cloud depends on the number of orbits in which the electrons are distributed. Electrons in the outer orbit – the valence orbit – easily enter into relationships with other atoms to form atomic and covalent bonds. The closer it is to the nucleus, the more energy the electron has. For the hydrogen atom – which is very often involved in reactions – the energy of the electron in the first orbit is minus 13.6 eV. The next electron shells are 1,2,3,4, etc. are the cardinal numbers **quantum**. An electron can change its orbit, but in order to move to an orbit closer to the nucleus, it must receive additional energy. Changing the orbit from 2 to 1 requires 3.4 eV. Such transitions are **quantized**, which means that the jump is either there or it is not – there is no intermediate possibility. If an atom in a molecule receives **quantum** energy from another atom or molecule, then the electron jumps to the orbit closer to the nucleus - its internal energy increases - in a step-by-step manner - **Quantized**. The so-called excited state of the atom is formed, which, unlike the ground state, is unstable. Such a state is unstable and immediately tries to return to the ground state by emitting 1 photon of energy – when the problem is the transition of 1 atom by 1 orbit. If we have countless such transitions in the molecule + odorant linkage, or transitions of 2 orbits or more, then there are 1020 possibilities of transmitting different types of **quantized** Energy. This results in a myriad and variety of odor information to be transmitted [6]. The odorant only transfers energy to the acceptor, not the chemical composition. The energy received by the acceptor is then transferred to the receptor and amplified, but cannot be changed. The combination of odorant and acceptor is unstable. If the odorant had not been disconnected from the acceptor, the receptor would have been permanently blocked. The tendency of an atom or molecule in an excited state to return to the ground state with the lowest energy, according to the principle of entropy, causes the transfer of energy further, and at the same time the loss of transmitted energy causes the detachment of the odorant molecule. Such a reaction in the case of very small molecules takes place over a period of 10^{-14} s. large molecules are detached up to 1000 times slower, but it is still 10 times $^{-11}$ s. The mechanism of detachment of the odor molecule from the acceptor is related to the concept of dissociation energy [6]. The OBP protein plays an important role in the transport of odorants in the nasal mucus and in odor detection. Mucus creates an aqueous environment on the surface of the mucous membrane in which specific interactions are formed, called the hydrophobic effect. The strongest hydrophobic effect occurs when molecules have both hydrophilic and non-hydrophilic areas. Such molecules easily interact with others, combine, electrostatic and hydrogen bonds are formed, dipoles are formed. These molecules are in constant motion. There are collisions of the odorant bound to the OBP protein and the temporary binding of the odorant to the receptor acceptor. The energy contained in the odorant molecule is transferred to the acceptor. The bond between the odorant and the acceptor is unstable and quickly dissociates due to dispersion forces. The strength of intermolecular bonds depends on the shape of the molecules, the number of hydrogen bonds, the number of atoms in the molecule, the size of the electron clouds and the dipole moments that are formed. Detached odor molecules from the acceptor and from the OBP protein are inactivated and destroyed by mucosal enzymes [7,8]. Olfactory information in the form of an energy packet from the donor reaches the acceptor, which is part of the receptor. The acceptor is where the odorant binds to the acceptor. The receptor is encoded in the nucleus of the olfactory cell, as a polyatomic molecule it can have many acceptors. The mechanism of information transfer from the acceptor to the GPCR protein occurs through the transfer of odorant energy causing conformational changes in the receptor associated with the G protein. Loop 3 of the outer GPCR binds the acceptor. The effect of stimulating GPCR is the phosphorification of GDP to GTP bound to the alpha unit of protein G. The phosphorylation reaction of GDP to GTP is an endothermic reaction and the energy is derived from the energy of the olfactory signal. The alpha subunit linked to GTP detaches from the beta and gamma units, having ATPase properties, stimulates adenylate cyclase, which causes 1 phosphate to detach from GTP. This is the energy source to change cytosolic

ATP into cAMP. The amount of cAMP molecules formed is proportional to the intensity of the olfactory signal. GDP formed from GTP, attaches to beta-gamma units and forms a new G protein that binds to the inner surface of the cell membrane with the GPCR receptor, it is ready to receive new information. Beta-gamma units stimulate Phospholipase C. The rate of these individual reactions is estimated to be 10^{-12} s. G-protein-related reactions are much slower [9,10].

An increase in the level of cAMP in the cell leads to the opening of cAMP-dependent calcium channels – it starts the depolarization of the olfactory cell. The conductivity of the cell membrane during depolarization increases several hundred times for sodium, the inflow of sodium ions into the cell through voltage-dependent sodium channels increases rapidly. When the equilibrium potential for sodium reaches zero, the sodium channels close and the potassium channels open, potassium flows out of the cell, ion pumps eject sodium ions outside the cell, cell repolarization occurs. At the top of the depolarization, the receptor potential is formed. This potential is always the same, maximum, because of the operation of the law of all or nothing. The magnitude of this potential is not dependent on the strength of the olfactory stimulus and cannot be treated as an action potential transmitted to the brain. [11,12].

Depolarization regulates the flow of Na+, K+, Ca++ and Cl- ions across the olfactory cell membrane, which are necessary for molecular transformations in the cell. The transfer of information to the center obtained from the odorant takes place by intracellular transformations ending with exocytosis of the transmitter to the synapse. The essence of this transmission is to activate energy transformations in the olfactory cell – leading to the interaction of the constitutive and regulated systems. The constitutive system is responsible for all processes related to cell life, just like all other cells [13]. The regulated system is responsible for the processes related to the transfer of energy towards the center. These systems work together, using the same substrates and enzymes [10]. The regulated system needs to be discussed. The energy transferred from the G protein is transferred to the nucleus of the cell and to other cell organelles. Proteins encoded in the nucleus involved in the transmission of information are produced, and second messengers in the cell are produced: ATP, cAMP, GTP, IP3, DAG. In an excitable cell like the olfactory cell, calcium is the fastest and cheapest second messenger.

The role of calcium in the olfactory cell

Increased levels of cAMP in the olfactory cell, caused by the activation of the G protein cooperating with the olfactory receptor, cause the opening of cAMP-dependent calcium channels. The influx of calcium ions into the cell is rapid due to the very high electrochemical potential of calcium on the cell membrane. The level of Ca++ in the olfactory cell is very low, around 100 nM/l. The level of calcium in the tissue fluid is about 1200000 nM/l. The level of calcium in the mucous membrane is unknown. Most of the calcium in the cell is stored in the endoplasmic reticulum and cell organs. The depolarization of the cell and the associated influx of calcium is a signal for its release from intracellular stores. An important factor here is IP3, produced when the G protein is stimulated. Calcium flowing through ion channels along with Ca++ released from cell stores quickly spreads inside the cell. An increase in the concentration of cytoplasmic calcium ions leads to their binding by specific proteins, which are thus activated, increasing the activity of various protein kinases [14].

In order for this mechanism to work, there must be a mechanism responsible for the very rapid reduction of calcium levels in the cell after depolarization and information transfer. This is done by a pump that carries the Ca2+ ion outside the cell in exchange for 2 H+ ions transferred into the cell. Ca2+H+ATPase is active here, drawing energy from ATP. The second mechanism that lowers calcium levels in the cell is antiport transport, dependent on the concentration of Na+ ions, which exchanges two Na+ ions from the extracellular space for one Ca2+ ion ejected outside the cell. The third mechanism is ion pumps that move calcium ions from the cell's fluids to organelles, mainly mitochondria, endoplasmic reticulum and nucleus. At low signal intensities, the elevation of calcium levels is small and the return to low levels is rapid. The lower the level of calcium before the signal is triggered, the greater the ability to differentiate small increases in intensity. The so-called "background law" is at work here, which is important in the perception of perithreshold stimuli.

Calcium is a regulator of many intracellular mechanisms, but its most important tasks include participation in the transmission of intracellular information, its strengthening and distribution. The

role of calcium is to influence Ca2+ ions on enzymes such as: adenylate cyclase, phosphodiesterase, phospholipase A2, protein kinase A. Calcium ions are the second messenger and are involved in the formation of other second messengers, such as cAMP, cGMP, IP3 and DAG.

Information transmission in the olfactory cell

The mechanical energy of the external signal, the odorant, which is only the trigger language of the cascade of intracellular reactions, triggers constitutive and regulated processes in the cell. Their intensity is proportional to the energy of the external signal. Intracellular information transmission pathways are activated. The second messengers are water-soluble and have the ability to move quickly through the cell. The processing of information in the cell and its transmission is related to the reversible formation and hydrolysis of phosphate-ester bonds. Kinases are responsible for the formation of bonds; phosphatases are responsible for hydrolysis. There are two types of kinases: tyrosine – forming phosphate esters on selected tyrosine residues of the substrate and serine-threonine, forming phosphate esters on selected serine or threonine residues. Each cell possesses a set of about 1000 different kinases, indicating that these kinases are major participants in intracellular signaling. Kinases are responsible for the phosphorylation of proteins, which change their conformation, become active and excite other proteins, creating a wave of activation of proteins of the signaling pathway. Phosphorylation is an "on-pass" operation, while phosphatases, which are the same number as kinases in the cell, work on the principle of "turn off, end of information".

There is the so-called specificity of kinases and phosphatases. They phosphorylate or remove phosphates from well-defined substrates. The transfer of information is an endoergic process, it requires the supply of energy from the breakdown of a high-energy compound, a universal energy donor – ATP or GTP. Two types of hydrolyzing enzymes are at work here: ATPases and GTPases, which are intracellular molecular switches. They are actively involved in the transmission of intracellular information and in most regulatory processes in the cell. The olfactory cell, just like the auditory cell [15], is an extremely complex device operating according to two programs: the first is related to the life of the cell as the basic unit of the organism, the second is related to the processing of information transmitted from the receptor. The two programs work together, often using the same information transfer pathways, the same substrates and the same enzymes. The functioning of the second program depends on the proper functioning of the first.

The signal energy from the odorant, converted into the electrical energy of the membrane potential, then converted into the chemical energy of the ionic and covalent bonds of the intracellular messengers, is amplified and distributed to both systems. The gain is greater the lower the energy of the external signal. High signal intensities are accompanied by adaptation and inhibition phenomena. The olfactory cell is a perfectly organized workplace, whose final product (transmitter) is a tool in the information transfer system. The production of the product and its storage is regulated by the first (constitutive) system, while the secretion of the transmitter into the synapse is part of the second system – regulated. These systems work closely together in the processing and transfer of energy in the cell. If an external signal of threshold intensity produces a potential of 10 on the membrane of the receptor cell, $^{-9}$ Volta, this energy must be amplified many times over in order to reach the central nervous system. The process of energy conversion and transfer is accompanied by the phenomenon of energy dissipation. Part of the signal energy is converted into thermal energy according to the laws of thermodynamics. The signal in the cell – a portion of energy – travels in the form of a wave at a rate of about 0.5 millimeters per second.

The most important task of the regulated system is the production, storage, packaging of the transmitter into synaptic vesicles and transport of vesicles to the presynaptic region. A molecular engine – kinesin – is responsible for anterograde transport. Dynein is responsible for retrograde transport – recycling of alveolar membranes after exocytosis.

Between the axon of the olfactory cell and the dendrite of the mitral cell **there is a chemical synapse**. Synapse action can be regulated by presynaptic or postsynaptic inhibition. When the energy for depolarization is too low, temporal summation or spatial summation occurs. At the synapse level, interneurons are turned on, information from interneurons is integrated and information is encoded for further transmission [15].

The energy transferred is proportional to the energy of the odorant, it can be amplified. An increase in calcium levels in the presynaptic region is a signal to release a portion of the transmitter into the synapse.

The amount of transmitter is proportional to the energy of the signal – to the energy that releases synaptic vesicles. These vesicles are transported by anterograde transport from the site of production in the endoplasmic reticulum and the Golgi apparatus to the presynaptic zone. At the signal, especially when calcium levels rise, calcium-activated proteins, such as gelsolin, break the protein bonds that attach the umbilical cord to the cytoskeleton. The protein complex in the presynaptic region facilitates the contact of vesicles with the presynaptic membrane, their fusion with the membrane and the formation of a channel connecting the inside of the vesicle to the synapse. The membrane that surrounds the vesicle has the same structure as all the membranes of the cell, it gets incorporated into the presynaptic membrane. The mass of the presynaptic membrane increases, but only for a short time, after which the built-in part of the alveolar membrane is separated and sent back by retrograde transport to the Golgi apparatus. Dynein is responsible for retrograde transport.

The secretion of the transmitter into the synapse is related to the transmission of information obtained by the receptor. The synaptic cleft, about 50 nm wide, is filled with fluid in which the transmitter moves from the presynaptic membrane to the postsynaptic membrane in 0.5 ms. After reaching the postsynaptic membrane, the transmitter connects to specific ion channels, causing them to open and depolarize the postsynaptic membrane. The transmitter is active only for a period of about 1 ms, after which it detaches from the ion channel due to the dissociation energy and is broken down by enzymes present in the synaptic cleft. As a result, post-synaptic membrane receptors are not blocked. Part of the transmitter can be moved outside the synapse. The level of transmitter decreases rapidly, after which ion channels become sensitive to its new influx. Usually, transmitters cause the opening of sodium channels, the influx of Na^+ ions into the postsynaptic region, which is the initial section of the afferent nerve of the next neuron. A depolarization potential, an action potential, is formed on the postsynaptic membrane. If a certain threshold of the signal causing depolarization is exceeded – about 15 mV – this depolarization travels along the afferent nerve to the next synapse. Multiple regulatory mechanisms are associated with synaptic transmission, such as pre- and postsynaptic inhibition and summation, spatial and temporal summation, enzymatic degradation, and transmitter resorption. Often, in addition to the basic transmitter, there is also a cotransmitter, which plays a regulatory role – it supports or inhibits the operation of the transmitter [16].

At the synapse, the energy of the chemical bonds of the transmitter is converted into the electrical energy of the action potential transmitted to the central nervous system. The process of encoding the transmitted information takes place in the synapse. Coding consists of arranging in a unit of time, the number and size of impulses in a nerve fiber or a bundle of fibers, depending on the information contained in the signal. In each successive synapse, the information is decoded, the electrical signal is converted into the chemical energy of the transmitter, the basic information reaching the synapse is integrated with additional information from the interneurons, the chemical energy is converted into the electrical energy of the action potential and encoded at the same time. After crossing several synapses and intersynaptic segments, information in the form of energy pulses reaches the central nervous system. It is decoded, subjected to an analysis similar to the Fourier analysis, and compared with the information stored in the persistent memory. An image of smell is created [8]. It takes about 100 milliseconds for the olfactory cell to process the information in the olfactory cell and transmit it to the synapse. Thousands of proteins are involved in the transmission of information. There are 10,000 proteins in a cell. Each of them has its own genetic code, splicing process, processing, half-life, and is subject to the laws of transcription, translation, post-translational processing, labeling, folding, transport, and decay in proteosomes and other cell organelles [16, 17]. Olfactory disorders may be the result of abnormal production or operation of nanostructures and nanoprocesses involved in the reception, processing and transmission of olfactory information. Understanding all the mechanisms of the olfactory pathway will be the basis for the implementation of new methods of diagnosis and treatment of olfactory disorders in the future.

Unfortunately, there is no complete knowledge about the number of olfactory cells in humans. The range of data is too large – from 5 to 50 million. The number of olfactory glomeruli ranges from 90 to 5,500, it doesn't matter, because the axons of olfactory cells connect synaptically with the dendrites of mitral cells, of which there are 60,000. Assuming an average number of olfactory cells in humans of about 20

million, one mitral cell receives information from 300 olfactory cells. But 1 olfactory cell has 8-20 hairs on the dendrite and there are an unknown number of receptors on each hair, and 1 receptor can have more than 1 acceptor. This shows how complicated the mechanics are at the level of nanoprocesses of reception and transmission of olfactory information. How difficult the path is for energy from the odorant to the central nervous system, overcoming several degrees of convergence.

Applications

The idea of this theory is based on three theses:

1. Total energy (kinetic, potential and electron), **Quantized**, is transmitted from the odorant to the brain, in contrast to Turin's theory, where only the energy of oscillation – kinetic energy – is taken into account.

2. Depolarization of the olfactory cell does not create an action potential. Depolarization works according to the law of "all or nothing" and cannot encode the sense of smell, there is no possibility **Binning** energy of the olfactory signal. The action potential arising on the postsynaptic membrane is proportional, consistent with the energy received from the odorant. Depolarization has to do with the electrochemical potential on the cell membrane and the transport of ions necessary for intracellular molecular transformations.

3. The most important energy transformations of the olfactory signal take place in the olfactory cell and in synapses on the way to the center, initiated by the receptor and the G protein. Calcium ions play an important role in the signal transmission in the olfactory cell.

Therefore, it is difficult to agree with the thesis that understanding the coding of olfactory receptors explains the whole problem related to our hearing, as the Nobel Commission ruled in 2004.

Abbreviations

H-2 - 2 hydrogen atoms
Oh - Angstrom 10-10 m
ATP – adenosine trophosphorane
ADP - adenozynodwuphosphoran
cAMP - cyclic adenosine monophosphate
Ca2+H+ATPase – calcium ion transporter
IP3 - inositol triphosphate
DAG - diacyloglycerol
PIP2 – phosphatidylinositol diphosphate
GPCR – G protein-related receptor
OBP – mucus protein that binds odorant
eV – electronVolt. nM/l–nanomol/liter

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