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Short Communication

Comments on the Theory of Smell

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INTRODUCTION

The human interest in the sense of smell dates back thousands of years. The first information on this question is found in Egyptian papyri. Sekhut Enanuch - the court physician of Pharaoh Sahure (5th Dynasty 2500-2300 B.C.) was a specialist in diseases of the nose, throat and ears. He was an otolaryngologist and dealt, among others, with the sense of smell. Democritus of Abdera (460-370 B.C.), the Greek philosopher believed that "the senses - color, sound, smell and taste, are secondary qualities, dependent on the internal structure of clusters of atoms." Democritus believed that "the world is composed of atoms and the vacuum around the atoms, which makes possible the movement of these atoms, their merging and splitting, the expansion of matter and the change of weight." Solomon, King of Israel (1000-931) believed that there were divine senses, attainable only to the chosen ones (blessed). These senses are eyes, ears, taste and smell - sensing odors pleasing to God that others do not experience. In the first century B.C., Roman philosopher Titus Lucretius Carus believed that odors are created by differences in the shapes and sizes of smells that stimulate the olfactory organ. This theory, called the theory of shapes, was approved and propagated in contemporary theories. Philosophers have argued for centuries about which of the senses is the most important. Sight was the absolute winner and confirmation came from the brain, where 1/3 of the cerebral cortex is associated with vision. (Bryson, 2019). For centuries, smell has been ignored and forgotten, despite being a sense precedent to sight. It develops from the 9th week of fetal life and after birth it is more important than sight. With the help of smell, a newborn recognizes mother, and Sniffing is used to find mother's breast during feeding. In the Subsequent years, sight plays a greater role. The issue of the effect of hormones on smell is an interesting subject. This is clearly sensed by women during their period. What is the molecular mechanism in the process of reducing the threshold of excitability under the influence of hormones? Olfactory information goes directly to the cerebral cortex. The sense of smell is the only sense organ that does not require the involvement of the hypothalamus [1]. The olfactory centers are very close to the hippocampus, where, among others, memories associated with smells are stored. The number of articles published worldwide on the subject of smell is several hundred per year. In contrast, tens of thousands of articles per year are published on the subject of vision or hearing. Research by Linda Buck and Richard Axel [2] between 1985 and 1991 regarding olfactory receptors, at the genetic level, led the scientists to conclude that a multigene family of genes encoding olfactory receptors is responsible for the reception of olfactory information. 339 complete genes encoding receptor proteins

have been identified in the human genome. The subsequent stages of the olfactory pathway have also been studied [3]. The Nobel committee optimistically stated, that the question of smell had been comprehensively dealt with once and for good [4]. However, there are many indications that the 2004 Nobel Prize-winning research has not solved all of the issues associated with smell. The novel and modern *quantum theory of smell* describes all processes down to the submolecular and electron level. It focuses not just on the genetics and functioning of the receptors, but states that an equally important role is played by the work of the olfactory cell itself and the synapses, which are the transmitters of information and the mechanism for encoding that information. The quantum theory draws attention to the significance of convergence in the transfer of information. Assuming that there are 10 million olfactory cells, derived from 339 genes, then there are approximately 300 groups of 30,000 homogeneous cells. The axons of the olfactory cells join together in bundles - they carry information to mitral cells. Receptors derived from the same genes bind to the same mitral cells, of which there are 60,000. If the published data is true, then one mitral cell receives information from 166 hair cells. Each cell has 8-20 microvilli, on each is an unknown number of receptors that receive olfactory information, and each receptor can have several acceptors. In addition, there are dozens of types of G protein genes, which also affects the transmission of information [5]. There is only one conclusion: With such convergence of information and complexity of the olfactory pathway, it is not possible to convey the structure, shapes and sizes of odorants and it is impossible to accurately assess changes in intensity through the diversity of olfactory receptors themselves. There is only one possibility - there is a transfer of quantized energy, which is the sum of all components received by the receptors. The number of possibilities for recognizing and discerning odor intensities is unlimited. The quantum theory of smell seeks to explain all olfactory mechanisms by assuming that it is the energy transferred from odorants that is subject to analysis in the brain. Evidence of the validity of the quantum theory of smell is the recognition of a single odor when 300 mixed odorous compounds act on the olfactory organ. This is what happens when we smell a rose flower, 300 fragrance substances act on the receptors at the same time.

Beforehand, that smell must be learned, realized and stored in permanent memory. Research by Prof. Andrew Horsfield of Imperial College, London, has confirmed the involvement of electrons in the transfer of energy from the odorant to the acceptor. Also, computer simulations by Dr. Jennifer Brookes of University College, London, have confirmed that our noses operate according to quantum chemistry in conveying information about the smell of various odorants. Research by Nobel Prize-winning U.S. scientists in 2004 did not manage to clarify all issues related to smell. Description of the formation of the action potential is lacking. The statement that depolarization of the olfactory cell creates an action potential is an unacceptable simplification. There is no description of the functioning of the olfactory cell, the role of the transmitter and the synapse, where the postsynaptic potential, the action potential, is formed on the postsynaptic membrane. Only the quantum theory of smell accurately describes all the energy transformations of the olfactory signal from the odorant to the brain. An example is the following abbreviated description of how the olfactory cell works. The physical, olfactory stimulus is transformed into an electrochemical signal. The kinetic, potential and electron energy of the odorant through the acceptor, receptor and G protein is transferred to the olfactory cell [6]. The odorant transfers to the acceptor only energy and not chemical composition. The odorant binding with the acceptor is unstable. If the odorant was not unbound from the acceptor, the receptor would be permanently blocked. The tendency of an atom or molecule in an excited state to return to the lowest-energy ground state, in accordance with the principle of entropy, results in the transfer of energy further and, at the same time, the loss of transmitted energy causes unbinding of odorant molecule. In the case of very small molecules, such a reaction takes place in 10^{-14} s. Large molecules unbind up to 1,000 times slower, but the time is still 10^{-11} s. The mechanism of unbinding of the odor particle from the acceptor is related to the concept of dissociation energy.

The OBP protein plays an important role in the transport of odorants in the nasal mucosa and in odor recognition. Mucus creates an aqueous environment on the surface of the mucosa, where specific interactions, called the hydrophobic effect, are created. The strongest hydrophobic effect is produced when molecules have simultaneously hydrophilic and non-hydrophilic

areas. Such molecules easily interact with others, combine, and electrostatic bonds, hydrogen bonds and dipoles are formed. These particles are in constant motion. There are collisions of odorant bound to the OBP protein and temporary binding of odorant to the receptor acceptor. The energy contained in the odorant molecule is transferred to the acceptor. Binding of the odorant to 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 resulting dipole moments. Odor molecules detached from the acceptor and from the OBP protein are inactivated and destroyed by mucosal enzymes. Olfactory information in the form of an energy packet from the donor reaches the acceptor, which is part of the receptor. The acceptor, is the binding site of the odorant and the acceptor. The receptor is encoded in the nucleus of the olfactory cell, and as a multi-atomic molecule it can have multiple acceptors [7]. The mechanism of information transfer from the acceptor to the GPCR protein is through the transfer of odorant energy causing conformational changes of the receptor bound to the G protein. Outer loop 3 of the GPCR binds the acceptor. The result of GPCR stimulation is the phosphorylation of GDP to GTP bound to the alpha unit of the G protein. The hosphorylation reaction of GDP to GTP is an endothermic reaction and the energy comes from the energy of the olfactory signal. The alpha subunit bound to GTP dissociates from the beta and gamma units, having ATPase properties, stimulates adenylyl cyclase, resulting in the dissociation of 1 phosphate from GTP. This is the energy source for changing cytosolic ATP into cAMP. The amount of cAMP molecules produced is proportional to the intensity of the olfactory signal. GDP formed from GTP, binds to beta/gamma units and forms a new G protein, which binds with the inner surface of the cell membrane with the GPCR receptor, ready to receive new information. Beta/gamma units stimulate Phospholipase C. The speed of these individual reactions is estimated at 10^{-12} s. G protein-related reactions are much slower [8]. An increase in cAMP levels in cell leads to the opening of cAMP-dependent calcium channels and an influx of calcium ions into the cell. The calcium level outside the cell is thousands of times higher than the calcium level inside the cell. The influx of calcium into the cell acts as a trigger and begins the depolarization of the olfactory cell. During depolarization, the conductivity of the cell membrane increases several hundred times for sodium, and the inflow of sodium ions into the cell through voltage-dependent sodium channels increases rapidly. Calcium continues to flow into the cell through voltage-dependent calcium channels. When the equilibrium potential for sodium reaches zero, sodium and calcium channels close and potassium channels open, potassium flows out of the cell, ion pumps eject sodium and calcium ions out of the cell, repolarization of the cell occurs. At the peak of depolarization, a receptor potential is formed. This potential is always the same, the maximum due to the operation of the "all or nothing" law. The magnitude of this potential is not dependent on the strength of the olfactory stimulus and cannot be considered as an action potential transmitted to the brain. Depolarization regulates the flow of Na+, K+, Ca++ and Cl- ions across the membrane of the olfactory cell, necessary for molecular transformations in the cell [9]. The transfer of information obtained from the odorant to the brain takes place through intracellular transformations ending with exocytosis of the transmitter to the synapse. The essence of this transmission is the activation of energy transformations in the olfactory cell - leading to the interaction of the constitutive and regulated systems. The constitutive system is responsible for all processes involved in the life of a cell, just like all other cells. The regulated system is responsible for the processes involved in the transfer of energy toward the brain. These systems work together, using the same substrates and enzymes. The regulated system needs to be discussed. The energy transferred from the G protein is transmitted to the cell nucleus and to other cell organelles. Nucleus-encoded proteins involved in the transmission of information are produced, second messengers in the cell are produced: ATP, cAMP, GTP, IP3, DAG. In excitable cell such as the olfactory cell, calcium is the fastest and cheapest second messenger.

These processes outlined briefly, vividly demonstrate the importance of connections between energy metabolism pathways and the pathways for processing and transmitting olfactory information in the cell. If we add genetic mechanisms, regulatory mechanisms of ion and proton pumps, the action of chaperones responsible for protein folding, and mechanisms of quality control of protein production in the ER (calnexin) to the

intracellular processes described here, it will be easier to understand the functioning of the olfactory organ at the level of the olfactory cell. A very important element in these considerations is the cell membrane of the olfactory cells. It's this cell membrane that creates the possibility of the existence of a potential difference between the interior of the cell and its surroundings. The resultant of the electrical and chemical gradient creates an electrochemical gradient, which determines the transport of ions across the membrane - it is the driving force for ions. Ion channels have voltage-dependent or agonist-dependent regulation. The sensitivity of voltage-dependent channels results from the channel's structure being electrically charged and responsive to depolarization. The movement of this sensor under the influence of a change in the electric field causes a change in the spatial arrangement of the channel protein called the gate. The openness of the channels creates the possibility of equalization of the electrochemical gradient on both sides of the cell membrane. The flow of each ion through the channel produces electric current flowing across the membrane, this is ion flow. The channel opening time is 1-2 ms. The time from the start of depolarization to the opening of the channel is 1 ms. Despite the continued depolarization, after 1-2 ms. opening, its inactivation occurs. This is a closed state of the channel and no stimulation is possible during this time. Only a drop in membrane potential causes the channel to move from its inactivated state to its usual closed state - susceptible to excitation. A protein called the inactivation gate is responsible for channel inactivation. Ligand-dependent (e.g., cAMP-dependent), or chemically activated, channels open when the appropriate agonist binds to the protein that forms the channel-opening mechanism. These channels occur in the olfactory cell. The third type of channels are sensitive channels and regulated by mechanical energy. These are receptors for the organs of touch, vision, hearing and the vestibular organ. In the nose, the chemical energy of odorants (via cAMP) causes conformational changes in the proteins of the calcium channel gating mechanism of the olfactory cell membrane, which initiates cell depolarization. Triggered by the adequate energy contained in the fragrance molecule, the avalanche of events results in the transmission of information thanks to the electrochemical potential at each step of the way. The dendrites of olfactory cells have 8-20 microvilli on each dendrite, which is the reason for the convergence of signals reaching the olfactory cell. In the case of convergence, a smaller stimulus causes excitation because numerous microvilli with a large number of receptors and an even greater number of acceptors stimulate a single olfactory cell. If we assume that the full cycle of opening and closing the sodium ion channel lasts 4-5 ms, then assuming that the depolarization involves the entire olfactory cell, the depolarization of the olfactory cell occurs every 4-5 ms. Depolarization of each olfactory cell may be at a different time. Integration of signals from individual neurons occurs in the olfactory bulb at the time of connection of I and II neurons, when the next signal convergence occurs. The process of depolarization and equalization of the electrochemical gradient is spontaneous and does not require external energy. Energy is required only for the initiation process, i.e. stimulation of calcium, sodium and potassium channels of the cell membrane. The entire sequence of events leads to depolarization of cells and an increase in the Ca level in the cells, and the calcium level determines further transformations in the olfactory cell. In the excitable - olfactory cell, the production, transport and secretion of transmitter into the synapse plays an important role. In the olfactory cell, transmitters are not described, but there must be a transmitter and perhaps a co-transmitter in the synapses between neuron I and II. The mechanism of the mediator's exocytosis cycle is always based on an increase in calcium levels in the cytoplasm of the presynaptic element after depolarization. The calcium level in the cell increases within 1 ms. causing exocytosis. Exocytosis is interrupted by rapid reduction of Ca^{++} levels by calmodulin, calcium transport out of the cell by ATPases, and co-transport dependent on Na^{+} ions. Some of the calcium moves into the endoplasmic reticulum, mitochondria and into the nucleus [10].

Linda Buck and Richard Axel's primary work was on the identification and coding of olfactory receptors. It should be remembered that 1,000 kinases and 1,000 phosphatases are involved in the work of the olfactory cell. There are approximately 10,000 proteins in an excitable cell such as the olfactory cell. Each protein has a specific role and each is encoded in the genome [10]. Transmitter is not specified? Is there a co-transmitter? Is there temporal summation and spatial summation? How does presynaptic inhibition work? Mucosal

electrolyte levels were not given. There is no description of the mechanism for encoding olfactory information. No description of the signal amplification mechanism. There is no description of the importance of calcium ions in the transmission of olfactory information. It is unclear whether the depolarization of the olfactory cell affects the entire cell at the same time? Is there local depolarization? The quantum theory of hearing explains most of these issues.

The Nobel prize committee announced already 20 years ago that everything about smell had already been explained. This was an overly optimistic statement.

ABBREVIATIONS

H-2 - 2 hydrogen atoms

Å - Angstrom 10^{-10} m

ATP - adenosine triphosphate

ADP - adenosine diphosphate

cAMP - cyclic adenosine monophosphate $Ca^{2+}H^{+}$ATPase - calcium ion transporter

IP3 – triphosforan inositol

DAG - diacyloglicerol

PIP_2 - phosphatidylinositol diphosphate

GPCR - G protein-related receptor

OBP – odorant binding protein eV - electronoVolt. nM/l - nanomol/liter

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