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20 Years after Nobel Prize Award for Smell

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Abbreviation:

H-2: 2 hydrogen atoms; Å: Angstrom 10-10 m; ATP: Adenosine triphosphate; ADP: Adenosine diphosphate; cAMP: Cyclic adenosine monophosphate; Ca2+H+ATPase: Calcium ion transporter; IP3: Triphosforan Inositol; DAG: Diacyloglicerol; PIP2: Phosphatidylinositol diphosphate; GPCR: G protein-related receptor; OBP: Odorant binding protein; eV: ElectronoVolt; nM/l: Nanomol/liter

1. Abstract

Smell is an important human sense and one that is the least understood. In some animals, it is the most important sense that determines survival on Earth. The first theory of smell was developed in the first century B.C. Roman philosopher Titus Lucretius Carus believed that differences in the shapes of "atoms" acting on the organ of smell, stimulate the organ. This theory has been called "shape theory." In modern times, several new theories of smell have emerged. Turin's theory, enhanced by electron tunneling, or the genetic theory of Laura Buck and Axel Richard do not satisfactorily explain all the processes involved in the reception, processing and transmission of olfactory information. 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 - about 20 bundles - to lead information to the mitral cells. So there are half a million axons in 1 bundle? 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 sensory hairs and on each hair 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.

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 just one possibility - there is a transfer of energy that is the sum of all the 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. Research by American scientists awarded the Nobel Prize in 2004 failed to explain all problems related to the question of smell.

2. The New Vision of Smell, Quantum Theory of Smell

Research by Linda Buck and Richard Axel [1,2] 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. In the human genome, 339 complete genes encoding receptor proteins have been identified [3,4]. The subsequent stages of the olfactory pathway were also studied. The Nobel committee optimistically stated that the olfactory problem has now been definitively solved. There are many indications that the 2004 Nobel Prize-winning research, in fact, has not managed to resolve all of the problems associated

with the sense of smell [5]. The new quantum theory of smell differs sharply from existing theories on several points. The basis of the theory is the reception and transmission of quantized energy from the odorant to the centers of the brain with proportionality, regardless of molecular transformations at the atomic and electron levels throughout the path of complex transformations.

The stimulus adequate for the olfactory organ is odor particle, which is a molecule containing from one to 17 million atoms. Every molecule as well as every atom in molecule is in constant motion. Bond length of hydrogen = 0.74 Å. The largest particle is 1μm long, 10 nm in diameter. It contains 17 million atoms, its molecular weight = 200 million Daltons. The length of atomic bonds undergoes constant lengthening and shortening due to vibrations of normal atoms. The atoms reach their maximum deflection at the same time. They undergo constant oscillatory and rotational vibrations and oscillations around their equilibrium positions. The vibration frequency is between 1013 Hz and 1014 Hz. The vibration period is on average 10-12 s. The oscillatory deflections are 10% of the bond length. For the hydrogen molecule H-2, it is approx. 0.1 Å. Each molecule has its own fundamental energy. External energy (odorant signal) causes a change in the potential energy of the acceptor and receptor, rotational excitation, a change in bond lengths, a change in covalent and torsional angles, a change in the total energy of the molecule and finally a change in the conformation of the acceptor molecule, which transfers energy to the G protein.

The kinetic energy of the molecule is associated with motion. In addition to kinetic energy, molecule has potential energy, which is represented by chemical bonds and the forces of electrostatic attraction and electromagnetic interactions. The sum of these energies forms the internal energy of the molecule's body. The internal energy also depends on the temperature and the mass of the molecule. Providing the external energy of the odorant to the acceptor molecule results in an increase in the acceptor's internal energy [6].

Odor particles (donors) have a positive or negative electrical charge or are neutral. Neutral particles transfer energy through the energy of molecular collisions and the merging of electron clouds of molecules. Every atom has electrons, which form an electron cloud, around the nucleus of the atom. The size of this cloud depends on the number of orbitals in which the electrons are distributed. Electrons in the outer orbital - the valence orbital - readily enter into bonds with other atoms to form atomic and covalent bonds. The closer to the nucleus, the greater the energy of the electron. For a hydrogen atom - very often involved in reactions - the energy of the electron, located in the first orbital, is minus 13.6 eV. Successive electron shells 1,2,3,4, etc. are the principal quantum numbers. An electron can change its orbital, but in order to move to an orbit closer to the nucleus, it must receive additional energy. Changing orbital from 2 to 1 requires 3.4 eV. Such transitions are quantized, which means that there is a jump or isn't - there is no middle ground. If an atom in a molecule receives a quantum of energy from another atom or molecule, the electron jumps to an orbital closer to the nucleus - its internal energy increases - in a quantized step. The so-called excited state of the atom is formed, which, unlike the ground state, is unstable. Such state is unstable and there is an immediate attempt to return to the ground state by emitting 1 photon of energy - when it's about the transition of 1 atom by 1 orbital. If in molecule + odorant binding we have an innumerable number of such transitions, or transitions by 2 orbitals or more, there are 1020 possibilities of transmitting different types of quantized energy.

This gives an innumerable amount and variety of transmitted information about odors [6]. The odorant transfers to the acceptor only energy and not chemical composition. The energy received by the acceptor, is subsequently passed on to the receptor, and amplified, but cannot be changed. 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 [6]. 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 [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 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. The mechanism of infor-

mation 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 phosphorylation 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 [9,10].

An increase in cAMP levels in cell leads to the opening of cAMP-dependent calcium channels - initiating 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. When the equilibrium potential for sodium reaches zero, sodium channels close and potassium channels open, potassium flows out of the cell, ion pumps eject sodium ions out of the cell, and cell repolarization occurs. At the peak of depolarization, a receptor potential is created. This potential is always the same, 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. [11,12].

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. 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 [13]. 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 [10]. 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.

3. The Role of Calcium in the Olfactory Cell

Increased level of cAMP in the olfactory cell, caused by activation of the G protein that cooperates with the olfactory receptor, results in 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 Ca++ level in the olfactory cell is very low, approximately 100 nM/l. The calcium level in the tissue fluid is approximately 1,200,000 nM/l. The level of calcium in the mucus membrane is unknown. Most of the cell's calcium is stored in the endoplasmic reticulum and cell organelles. Depolarization of the cell and the associated influx of calcium is a signal for its release from intracellular stores. An important factor in this is IP3, produced after stimulation of the G protein. Calcium flowing in through ion channels along with Ca++ released from cellular stores rapidly diffuses 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 very rapid reduction of calcium level in the cell after depolarization and transmission of information. Responsible for this is a pump that carries the Ca2+ ion out of the cell in exchange for 2 H+ ions transported into the cell. Ca2+H+ATPase works here, deriving energy from ATP. The second mechanism that reduces the level of calcium 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 increase in calcium levels is small and the return to low levels is rapid. The lower the calcium level before the signal is triggered, the greater the ability to discriminate between small increments of intensity.

The socalled "background law" is at work here, and it has significance in the perception of perithreshold stimuli. Calcium is a regulator of many intracellular mechanisms, but among its most important tasks is participation in the transmission of intracellular information, its amplification and distribution. The role of calcium is to influence Ca2+ ions on enzymes such as adenylyl cyclase, phosphodiesterase, phospholipase A2, protein kinase A. Calcium ions are second messengers and are involved in the formation of other second messengers such as cAMP, cGMP, IP3 and DAG.

4. Transmission of Information in the Olfactory Cell

The mechanical energy of the external signal, the odorant, which is only the trigger for a cascade of intracellular reactions, triggers constitutive and regulated processes in the cell. Their intensity is proportional to the energy of the external signal. Intracellular in-

formation transfer pathways are activated. The second messengers are water-soluble and have the ability to move rapidly in the cell. Information processing in the cell and its further transmission is associated with the reversible formation and hydrolysis of phosphate-ester bonds. Kinases are responsible for bond formation, and phosphatases are responsible for hydrolysis. There are two types of kinases: tyrosine kinases, which form phosphate esters on selected tyrosine residues of the substrate, and serine/threonine kinases, which form phosphate esters on selected serine or threonine residues. Each cell has a set of approximately 1,000 different kinases, indicating that these kinases are major participants in intracellular signaling. Kinases are responsible for the phosphorylation of proteins that change their conformation, become active and stimulate subsequent proteins, creating a wave of activation of proteins in the signaling pathway. Phosphorylation is a "turn-on and pass-on" type of action, while phosphatases, of which there are as many as kinases in the cell, act on a "turn off, no more information" basis.

There is the so-called specificity of kinases and phosphatases. They phosphorylate or remove phosphates from well-defined substrates. The transmission of information, is an endoergic process, requiring the supply of energy from the breakdown of a high-energy compound, the universal energy donor - ATP or GTP. Two types of hydrolyzing enzymes are at work here: ATPases and GTPases, which are proteins that are intracellular molecular switches. They take an active part in the transmission of intracellular information and in most regulatory processes in the cell.

An olfactory cell, like an auditory cell [15], is an extremely complex device that operates according to two programs: the first one is related to the life of the cell as the basic unit of the organism, and the second one 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 operation of the first one. The signal energy from the odorant, converted into electrical energy of the membrane potential, subsequently converted into chemical energy of ionic and covalent bonds, intracellular messengers, is amplified and distributed to both systems. The greater the amplification, the lower the energy of the external signal. High signal intensities are accompanied by adaptation and inhibition phenomena.

Olfactory cell is a perfectly organized workplace, whose final product (transmitter) is a tool in the information transmission system. The generation of the product and its storage are regulated by the first (constitutive) system, while the secretion of the transmitter into the synapse is a part of the second - regulated system. These systems work closely together in the conversion and transmission of energy in the cell. If an external signal with a threshold intensity produces a potential of 10-9 Volts on the receptor cell membrane, this energy must be amplified many times 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. A signal in cell - a portion of energy - travels as a wave at a speed of approximately 0.5 millimeter per second. The most important task of the regulated system is the production, storage, and packaging of transmitter into synaptic vesicles and transport of vesicles to the presynaptic area. The molecular motor - kinesin is responsible for anterograde transport. Dynein is responsible for retrograde transport - recycling of vesicular membranes after exocytosis.

There is a chemical synapse between the axon of the olfactory cell and the dendrite of the mitral cell. Activity of synapse can be regulated by presynaptic or postsynaptic inhibition. With too little energy for depolarization, temporal summation or spatial summation occurs. At the synapse level, interneurons are turned on, information from interneurons is integrated and information sent further is encoded [15]. The energy transferred is proportional to the energy of the odorant, and can be amplified. An increase in calcium levels in the presynaptic area is a signal to release a portion of the transmitter into the synapse. The amount of the transmitter is proportional to the signal energy - to the energy releasing synaptic vesicles. These vesicles are moved by anterograde transport from their place of generation in the endoplasmic reticulum and Golgi apparatus to the presynaptic zone. In response to a signal, especially by an increase in calcium levels, calcium-activated proteins like gelsolin break the protein bonds that attach the vesicles to the cytoskeleton. A complex of proteins in the presynaptic area facilitates the contact of vesicles with the presynaptic membrane, their fusion with the membrane and the formation of a channel connecting the interior of the vesicle to the synapse.

The membrane surrounding the vesicle has the same structure as all the cell's membranes, it becomes embedded in the presynaptic membrane. The presynaptic membrane mass increases, but only for a short time, after which the embedded part of the vesicle 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 received by the receptor. The synaptic gap, approx. 50 nm wide, is filled with fluid, in which the transmitter moves from the presynaptic to postsynaptic membrane in 0.5 ms. Upon reaching the postsynaptic membrane, the transmitter binds to specific ion channels causing them to open and depolarize the postsynaptic membrane. The transmitter is active only for a period of approx. 1 ms, after which it is dissociated from the ion channel due to dissociation energy and is degraded by enzymes present in the synaptic gap. Thanks to this, there is no blockade of post-synaptic membrane receptors. Part of the transmitter can be moved outside the synapse. The level of transmitter drops rapidly, after which the ion channels become sensitive to its new influx.

Typically, transmitters cause the opening of sodium channels, the

influx of Na+ ions into the postsynaptic area, which is the initial section of the afferent nerve of the next neuron. A depolarizing potential, an action potential, is created on the postsynaptic membrane. If a certain signal threshold that induces depolarization is exceeded - approx. 15 mV - this depolarization travels along the afferent nerve to the next synapse. Many regulatory mechanisms are associated with synaptic transmission, such as presynaptic and postsynaptic inhibition and summation, spatial and temporal summation, enzymatic degradation and transmitter reabsorption. Often, in addition to the primary transmitter, there is a cotransmitter, which plays a regulatory role - it supports or inhibits the transmitter [16]. At the synapse, the energy of the transmitter's chemical bonds is converted into electrical energy of the action potential transmitted to the central nervous system. At the synapse, the process of encoding the transmitted information takes place. Coding involves ordering the number and size of impulses in a nerve fiber or fiber bundle in a unit of time, depending on the information contained in the signal. In each subsequent synapse, 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, and the chemical energy is converted into electrical energy of the action potential with its simultaneous coding. After crossing several synapses and inter-synaptic sections, information in the form of pulses of energy reaches the central nervous system. It is decoded, subjected to an analysis similar to Fourier analysis and compared with the information stored in permanent memory. An olfactory image is formed [8].

It takes about 100 milliseconds to process information in an 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 has its own genetic code, splicing process, processing period, half-life, and is subject to the laws of transcription, translation, post-translational processing, labeling, folding, transport and degradation in proteosomes, or other cellular organelles [16,17]. Olfactory disorders can result from abnormal production or operation of nanostructures and nanoprocesses involved in receiving, processing and transmitting olfactory information. Understanding all the mechanisms of the olfactory pathway will be the basis for implementing new methods of diagnosis and treatment of olfactory disorders in the future.

Unfortunately, there is no complete knowledge of the number of olfactory cells in humans. The spread of data is too large - from 5 to 50 million. The number of olfactory glomeruli ranges from 90 to 5,500, but it does not matter, because the axons of olfactory cells synaptically connect with the dendrites of mitral cells, of which there are 60,000. Assuming that the average number of olfactory cells in humans is approximately 20 million, one mitral cell receives information from 300 olfactory cells. But 1 olfactory cell has 8-20 hairs on dendrite and each hair has an unknown number of receptors and 1 receptor can have more than 1 acceptor.

This shows how complex the mechanics are at the level of nanoprocesses for receiving and transmitting olfactory information. What a difficult path the energy travels from the odorant to the central nervous system, overcoming a convergence of several steps.

5. Conclusions

The idea behind this theory is based on three theses:

1. Total energy (kinetic, potential and electron), quantized, is transferred from odorant to the brain, unlike in Turin's theory, where only oscillation energy - kinetic energy - is considered.

2. Depolarization of the olfactory cell does not create an action potential. Depolarization works according to the "all-or-nothing" law and cannot encode smell, there is no way to quantize the energy of the olfactory signal. The action potential generated at the postsynaptic membrane is proportional, consistent with the energy received from the odorant. Depolarization is related to the electrochemical potential on the cell membrane and the transport of ions necessary for intracellular molecular changes.

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

Therefore, it would be hard to agree with the thesis that understanding of the coding of olfactory receptors settles the matter of our hearing, as the Nobel prize committee stated in 2004.

References

1. Buck L, Axel R. A novel multigene Family may encode odorant receptors. A molecular basis for odor recognation. Cell. 1991; 65-175.
2. Malnic B, Godfrey PA, Buck LB. Human olfactory receptor gene family. Proc. Natl. Acad. Sci. USA. 2004; 101: 2584-89.
3. Obrębowski A. Nobel Prize in Physiology or Medicine for 2004, Practical Medicine. 2005; 3-35.
4. Obrębowski A. Outline of Clinical Olfactology and Gustometry 2022, Medical University of Warsaw Karol Marcinkowski in Poznań str. 11-22.
5. Skargiel-Kremska J, Rogozińska K. Sense of smell-Coding odors. Space-Problems of Biological Sciences, Nobel Prize in Physiology or Medicine w 2004 r. Tom 54, 2005, Nr 2-3, (267-268), str. 149 -154.
6. Piela L. Ideas of quantum chemistry, PWN, Warsaw 2022; str. 1300.
7. Repetowski M, Kuśnierczyk K, Mazurek A, Mikulska J, Olszewski J. Neurological News 2010, Basics of the anatomy and physiology of the olfactory pathway and the possibilities of topodiagnosis of its damage using olfactory evoked potentials. 10(2): 85-88.
8. Zmorzyński S, Popek S, Koczkodaj D, Filip A. Genetic and biochemical aspects of the sense of smell, Advances in Cell Biology, Department of Cancer Genetics with the Cytogenetic Laboratory of the University of Lublin, Tom 41. 2014; 4: 583-598.

9. Kristiansen K. Molecular mechanisms of ligand binding, signaling, and regulation within the superfamily of G-protein-coupled receptors: molecular modeling and mutagenesis approaches to receptor structure and function. Pharmacol Ther. 2004; 103(1): 21-80.
10. Matthews HR, Friedland RA, Miesfeld RL. Biochemistry and Molecular Biology, Prószyński i Spółka, Warszawa. 2000; r. Str. 530.
11. Barańska J, Kłopocka W. G proteins – Role in signal transduction: Cell signal transduction pathways. Nalepa I. (ed.). 21st Winter School of the Institute of Pharmacology of the Polish Academy of Sciences, Mogilany. 2004; 17–27.
12. Myjkowski J. Submolekular Theory of Hearing, HSOA Journal of Otolaryngology Head and Neck Surgery. 2022; 8: 069.
13. Fuller GM, Shields D. Molecular foundations of cell biology, medical aspects. PZWL, 2000; Warszawa. Str. 255.
14. Young PA, Young PH, Tolbert DL. Clinical neuroanatomy Ed. 3, Edra Urban & Partner, Wrocław 2016.
15. Myjkowski J. Submolekular Theory of Hearing, HSOA Journal of Otolaryngology Head and Neck Surgery. 2022; 8; 069.
16. Matthews GG. Neurobiologia, PZWL Wydanie I, Warszawa, 2000; r. str. 600.
17. Alberts B, Bray D, Johnson A, Lewis J, Raff M, Keith R, et al. Fundamentals of Cell Biology, PZWL 1999; 690.