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Short Communication

# Our Sense of Smell

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## Abstract

Smell is one of the most highly developed senses in some insects, animals and fish. It conditions the survival of species on Earth. It serves to locate the food source, senses danger and helps to find a partner to extend the species. With the help of smell, individuals communicate with each other. The smell of the insect, the silkworm, is excellent. The male recognises in the air single particles of an odorous substance secreted by the female from a distance of 10 km. Fish use their sense of smell and memory in their journeys of thousands of kilometres from rivers to seas. A shark can smell blood in the water from several kilometres away. Ants leave an olfactory trail for their brethren, indicating a food source, or leave a "death scent" when they warn of danger. Man, not having such a good sense of smell, uses dogs with 10 times better sense of smell to track down drugs or criminals. The record-holder among sniffers is the male nocturnal peacock butterfly (Eudia Paonia), which can smell the pheromones of a female from a distance of 11 km, when the signal produced has only 0.0001 mg of scent per dose. The signal sent by the female into the ether is perfectly produced molecules according to her own code. The partner has a specific coded receptor and reads the transmitted information. Butterflies do not have a nose, the olfactory cells are located on the antennae and further information is transmitted to the central nervous system, where it is analysed. The paper highlights the molecular basis of olfactory information transmission and reception.

**Kew Words:** adenosine triphosphate; carbon dioxide; inositol triphosphate

## Abbreviations:

H-2 - 2 hydrogen atoms
Å - Angstrem $10^{-10}$ m
Nm - nanometre $10^{-9}$ m
Hz - Hertz
ATP - adenosine triphosphate
ADP - adenosine diphosphate
cAMP - cyclic adenosine monophosphate
IP3 - inositol triphosphate
DAG - diacylglycerol
$CO_2$ - carbon dioxide
$PIP_2$ - phosphatidylinositol diphosphate

## Introduction

In the first century BC, the Roman poet and philosopher Lucretius (Titus Lucretius Caruso c. 99 BC - 55 BC) believed that odours were created by differences in the shapes and sizes of the 'atoms' that stimulate the organ of smell. This was the 'theory of shapes'. There are many indications that Lucretius got a lot of things right. Research on the sense of smell was carried out by Americans Richard Axel and Linda Buck from 1980 onwards. The announced their work in 1991 and were awarded the Nobel Prize in 2004. The work was mainly concerned with which neural pathways information about a particular odour reaches the brain. The second major topic concerned the coding of odour receptors in the olfactory organ [1]. The authors state "that all olfactory receptors belong to a superfamily of proteins having seven transmembrane domains and are coupled to G proteins. Secondary messengers are formed, and the conductance of membrane ion channels is altered. It is assumed that only one olfactory receptor gene is expressed in the olfactory neuron. The question arises: How are thousands of odorous substances, which have a similar structure but give a completely different odour sensation, recognised. It was therefore assumed that one receptor could recognise multiple odour substances. Furthermore, it was assumed that one odorant can be recognised by many receptors. It was concluded that there is a complex receptor code. According to this code, a specific odour substance stimulates a defined set of neurons, each of which has only one type of receptor [2]. In the first stage of sensory information processing in the olfactory epithelium, the information carried by odorous substances is analysed. A given odorous substance stimulates a specific combination of olfactory neurons in the nasal cavity." The authors showed that there is only one type of receptor on a single olfactory cell, which is able to detect several different odour molecules.

Is this substantiated?

### Our sense of smell

It has been 32 years since the Nobel laureates published their work describing the mechanisms of the olfactory organ [3]. During this time, there have been tremendous advances in quantum chemistry, allowing a better understanding of the processes that make up the reception, processing, and transmission of olfactory information [4,5]. These processes take place at the sub molecular and subatomic level. They are very complex and extremely interesting [6]. Organic molecules - as olfactory signals - are multi-atomic and have numerous proton and electron donors and acceptors. Sometimes one side of a molecule has a whole system of donors and acceptors. Such an arrangement waiting to be paired with a competent acceptor is called a synthon. The donor of a molecule has free pairs of electrons on its surface waiting for a positive acceptor ion, and in addition has similar dimensions. If the dimensions of the donor and acceptor are ideal or close to ideal, it is a lock-and-key combination - known and described in allergology and immunology for 100 years. If the donor has to match the dimensions of the acceptor - it is a template (rack) connection. Molecular recognition occurs when the donor molecule adopts a new conformation with a higher energy than in the original donor conformation. If the donor and acceptor have to change conformation before joining - this is a hand-in-glove connection. This is energetically disadvantageous. Each molecule is made up of nuclei of positively charged atoms, connected by ionic, covalent or hydrogen bonds, forming different angles (valence-flat, between bonds, torsion-double bond, between bonds). Negatively charged electrons circulate in different orbits of the atom, having their own energy and spin. The nucleus of an atom with a size of $10^{-15}$ m consists of protons and neutrons. Other constituents of the atom are: quarks, antiquarks, mesons, leptons, baryons, bosons, fermions and gluons. Electrostatic and magnetic interactions between atoms play a certain role. Opposite charges attract each other even from a great distance, univalent charges repel each other. Each atom has electrons, orbiting the nucleus in their own orbits. The binding energy depends on the electron energy, which consists of the orbital angular momentum with the intrinsic angular momentum or spin. The binding energy of the donor to the acceptor is equally -weighted with the dissociation energy necessary to separate the donor and acceptor after the transfer of information. Otherwise, the acceptor would be permanently locked. The size range of olfactory molecules is gigantic. The smallest hydrogen molecule, H-2, contains 2 protons and 2 electrons and has a molecular mass of 2 Daltons. Its bond length = 0.74A. The largest molecule is 1µm long, 10 nm in diameter. It contains 17 million atoms and has a molecular weight = 200 million Daltons. Atomic bond lengths undergo constant lengthening and shortening due to the normal vibrations of the atoms. The atoms reach their maximum deflections at the same time. They perform constant rotational vibrations and vibrations around their equilibrium positions. The frequency of vibration is between $10^{13}$ Hz and $10^{14}$ Hz. The period of vibration is on average $10^{-12}$ s. The vibrational deflections are 10% of the bond length. For the hydrogen molecule H-2 this is about 0.1 Å. Each molecule has its own fundamental energy. The external energy (signal) causes a change in the potential energy of the acceptor (receptor), rotational excitation, a change in bond length, a change in valence and torsional angles, a change in the total energy of the molecule and finally a change in the conformation of the acceptor molecule. Receipt of information by the receptor leads to the activation of a specific trans-membrane protein G, seven times across the receptor cell membrane. The G protein activates adenylyl cyclase, which catalyses the conversion of ATP to cAMP and this initiates a series of reactions in the olfactory cell. Signalling molecules play an important role: ATP, cAMP, IP3, DAG and Ca++ that regulate the activity of intracellular target molecules: Calcium levels in the cell increase, ion channels of the cell membrane work, depolarisation of the cell occurs. In an excitable cell such as the nerve and auditory cell, a transmitter is produced, packed in portions into synaptic vesicles, transmitted to the synapse, where the chemical energy of the bonds is converted into electrical energy. An excitatory potential is created and, in excitable nerve cells, an action potential is formed, which is conducted via nerves to the central nervous system. In bipolar olfactory cells, transmitters have not been described. To understand these processes, elements of quantum chemistry are taken into account, playing an important role in the molecular transformations of smell: Oscillatory levels, rotational excitation, rotational levels, potential energy for the motion of nuclei, electron excitation, electron ground state, harmonic oscillator, resonant state, rotational potential, bond energy, normal vibration. Since the final results of translation, rotation, vibration and other actions depend on the signal's own variables, the final result is the sum and partly the product of the individual actions. In contrast, the total energy of the signal after reception is the sum of the translational, electron, rotational and oscillatory energies. At the slightest approximation of the molecules, there is a valence interaction associated with the overlap of the electron clouds of the two molecules. This is a repulsive effect, increasing rapidly with excessive proximity. Valence interactions are very important in being able to specifically match spatially approaching molecules, which is crucial in molecular recognition: signal - receptor. The chemical reaction to connect the donor (signal) to the acceptor (receptor) occurs when the forces seeking to connect outweigh the valence interaction. The reaction barrier must be overcome, which determines the specificity of the signal-receptor reaction. There are changes in the occupancy of the acceptor orbitals by electrons. This causes a change in the electron hypersurface, a change in the energy of the acceptor (receiving the signal), conformational changes, changes in the vibration of the atoms and the molecule as a whole and finally the transmission of the signal from the olfactory cell membrane receptor to the cell interior via the trans-membrane G protein. The resonance of vibrations of atoms and whole molecules, and the resonance of atomic bond vibrations play a certain role in the transmission of signal energy. The transmitted signal energy is quantised, i.e., it is a multiple of a full number of 1 energy quanta. This is exactly the same as in the organ of hearing or sight, where the energy transfer is quantised [4]. The external signal heading for the receptor is a type of energy of different kinds for the different senses. For hearing, it is the mechanical energy of a sound wave [7]. For smell, it is energy encoded in molecules, ions or even atoms reaching a specific receptor. In the olfactory organ, metabotropic receptors that recognise chemical molecules - ligands, called molecules - predominate by far. It is thought, perhaps incorrectly, that the olfactory organ uses only metabotropic receptors that bind to G-proteins on the inner side of the cell membrane of the olfactory cells. Olfactory recognition of hydrogen sulphide, oxygen, $CO_2$, or acidic environments can hardly be linked to the metabotropic receptor and G protein. The new signal-specific energy acts on trans-membrane proteins that pass 7 times through the membrane of the olfactory cell - the G proteins. The transferred energy inside the cell acts on a variety of proteins and chemicals linked to the α β γ subunits of the G protein: (adenylate kinase, ADP, ATP, phospholipase C-PLC, phospholipase A -$PLA_{22,}$ cAMP, IP $kinase_3$ -inositol triphosphate kinase, protein kinase-A - PKA, other kinases and phosphatases, calcium binding proteins - calmodulin. Ca++ plays a major role in the cell. Protein kinase C - PKC plays a role in the transcription of genes in the cell, also olfactory receptor genes. A membrane potential is formed, Na, K, Ca, Cl ion channels work. Ion pumps and ion transporter's function. The mechanism of intracellular signalling is working efficiently, communication pathways are being established. All this contributes to the mechanisms of processing and transmission of olfactory information in the olfactory cell. Ligand-receptor binding acts on the α β γ molecule of the G protein trans-membrane. With the involvement of tyrosine kinase, PIP hydrolysis $occurs_2$ , followed by the formation of second-order informants: $IP_3$ , DAG, which initiate the Ca++ signalling pathway. $IP_3$ binds calcium channel proteins causing the channel to open, allowing Ca++ ions to flow into the cell from the environment and from the stores of the endoplasmic reticulum, nucleus and mitochondria by force of the concentration difference on both sides of the membrane. Ca++ levels must not increase excessively in the cell. At a certain point, excess Ca++ in the cell causes activation of the IP phosphatase $kinase_3$, resulting in closure of calcium channels and activation of the mechanism to remove Ca++ ions from the cell to the outside and to the endoplasmic reticulum, nucleus and mitochondria. The cell only responds to the signal at low calcium levels inside the cell, thousands of times lower than outside the cell. Calcium activates calmodulin, which binds specific kinases and stimulates a signalling cascade, affecting multiple signal amplification. The problem that remains to be clarified is how intracellular molecular changes and depolarisation of the olfactory cell leads to the formation of an action potential, conducted to the brain. In the organ of hearing, intracellular transformations lead to the production and secretion of transmitter into the synapse, where a postsynaptic excitatory potential is formed that is conducted to the nerve cells of the spiral ganglion, and it is only here that an action potential is formed [7]. In the olfactory organ, the transmitter was not described; the whole focus of the Nobel laureates was mainly on genetics, the G protein and the pathway of the action potential to the brain. A very important step in the pathway of the olfactory signal to the centre - in the olfactory cell itself - was omitted.

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