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The relationship among biological membranes and signaling mediators. I. How can this be explained?

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Summary. In this paper I briefly reviewed the relevance of a membrane structure to biological signal systems in the light of current knowledge. Also this paper deals with some of the features of biological membranes that are related to functions that they perform in the living cells. I describe how are conjoined between themselves fatty acids in the membrane layer. The discussed data have been chosen with the advances of our understanding of the membrane molecular organization and their role in the perception of signals, transformation and transduction them to targets and response pathways. One of the outstanding conundrums concerning the perception mechanism is how this process deals with genomic and non-genomic responses.

Keywords: lipids, membranes, oxidants, receptors, signaling.

Introduction. In nature multicellular plant and animal organisms are exposed to various abiotic and biotic stresses. Extremes temperatures (freezing, cold and heat), water availability (drought, flooding), and ion toxicity (salinity, heavy metals, several pollutants) represent abiotic stress. A biotic stress factors are presented by various pathogens, fungi, bacteria, viruses and insects. The life of cells depends on their ability to transform a wide variety of intracellular and extracellular signals into the suitable ways, which in general are close connected with cell membrane structures.

This paper provides an overview of what is known about the relationships among biological membranes and signaling molecules and discuss the data that link membrane structures to the signal transduction which permit the living organisms to survive in perturbed environments.

Also our aim here is to highlight the findings in signaling pathways that can provide some insight into the molecular mechanism of signal transduction in the living things.

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What role do the membrane structures play? A biological membrane in accordance to fluid mosaic model [7], is a two-dimensional fluid of oriented proteins and lipids. The basic structure of all cell and organelle membranes is the lipid bilayer. Fluid properties of biological membranes are determined mainly by the presence of polyunsaturated fatty acids in phospholipid molecules.

Evidence is provided that biological membranes are vitally important structures, at which important biological processes occur and they mediate the communication exchange between the cell and the environment or other cells. Also, cell membranes are essential barriers to separate intracellular and extracellular space. In this connection knowledge of their higher order organization and interaction with external and internal stimulus is of great interest.

Biological membranes are composed of different lipids and proteins and provide the structures that function as a platform for the assembly of many signal transduction pathways. Cellular membranes are composed from 30 to 80 % of lipid molecules by mass, 20-60 % of proteins and 0-10 % of carbohydrates [2].

It is generally agreed that the polyunsaturated fatty acids determine the fluid properties of

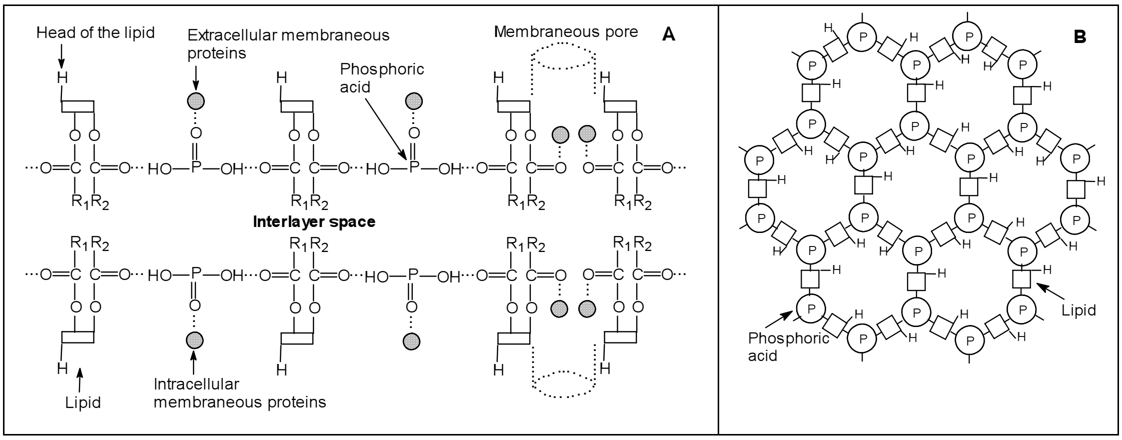

Fig. 1. Schematic representation of the lipid packing in the biological membranes. (A) Viewed in a cross section of the membrane. (B) Viewed from top on the membrane layer. Individual lipids of the monolayer are conjoined into hexagonal structures by phosphoric acid (by hydrogen bonds).

cellular membranes. Unfortunately, regardless of many published papers, is also incomprehensible how unsaturated fatty acids determine these properties.

Nothing is also known how lipids are associated between themselves to form the regular monolayer. Are end-methyl groups of a flexible acyl tail of fatty acids from two opposing lipid layers free, or combined one with other? At the same time it is not clear why exactly polyunsaturated fatty acids are needed to form the optimal membrane structures.

It is no clear how might be conjugated two fatty acids from opposed membrane layers. If fatty acids of two leaflet are not combined one with another, hence fatty acids are not constrained in their moving and turning. This means that membrane bilayers should form the cavities like a retort of different sizes, but electron micrographs do not reveal very amounts of structures like a retort. Nevertheless, there are very important formations in the plasma membrane named as lipid rafts and caveolae, that differ from the rest of the membrane by physic-chemical properties.

An alternative opinion on the membranous lipid bilayer function. It is suggested that the biological function of lipids in the plant and animal cells is manifold. With information mentioned above, the following question arises: How strongly conserved is the function of membranous lipids? It is generally agreed that biological membranes are composed of two lipid bilayers. In such structures the methyl groups of tails of fatty acids of both layers are arranged in opposed from one direction to another. The methyl groups of fatty acids are inert radicals and cannot react between themselves. Nevertheless, the stability of membrane layers is very strong and cannot be destroyed, for example, by higher concentrations of salts. In this connection the next questions arise: How are lipids retained together in the monolayer? Are the methyl groups of two layers contacted between themselves?

We propose a model for lipid packing in the biological membranes (Fig. 1) [4]. The basic idea of this model (termed as «a double net model») is that individual lipids are bonded between themselves by phosphoric acid. The space between two opposing monolayers is free of any reactive chemicals and may serve as a tunnel for traffic of diverse substances to diverse compartments of the cell (Fig. 1A). Single lipids of the monolayer are conjoined into hexagonal structures by phosphoric acid with hydrogen bonds (Fig. 1B). In the rafts and caveolae can be presented diverse antioxidants, including cholesterol, reparative and antioxidative enzymes, unsaturated fatty acids, nucleic acids, ATP, FADH, $NADP^+H$, etc.

Signaling agents and transduction systems: How do they signal and what are their targets? All living organisms possess in signal transduction systems that may differ by nature in animals and plants. At least two types of signals are presented: (1) signals from outside the cell (extracellular signals) to inside initiate the intracellular signaling pathways and (2) signals between molecules inside a cell. It is generally believed that all signals received by the cell first interact with a receptor, embedded in either the plasma membrane or the cytoplasm of the cell [1, 10]. Thus, the receptors may be the sensitive substances that absorb physical or chemical factors and start the processes that send signals to cellular membranes or nucleus.

When the cell received the internal or external stimuli there are two ways for further signaling events: «genomic» signaling and «non-genomic» or «rapid» signaling [5]. Genomic signals bring about their biological effects through interactions with specific receptors, mostly related to the nuclear receptor family [8]. Non-genomic signaling is equated with membrane initiated signaling. Nevertheless, the membrane signaling events may lead secondarily to the modulation or initiation of transcriptional activity. Hence, the distinction between these physiological and cellular responses is times misleading, and can be determined by nature of the stimulus.

Signaling processes during various stresses are frequently accompanied by simultaneous increase in the activation of oxidative reactions (free radical reactions), which cause injure to nucleic acids, proteins, structural carbohydrates, and lipids [6].

As mentioned above polyunsaturated fatty acids and their metabolites also have a role of cell signaling and regulation of the gene expression. Membrane lipids containing polyunsaturated fatty acids are susceptible to oxidation and this can occurs in response to such process as an oxidative stress.

Cells react defensively by initiating several signal transduction pathways that result in the accumulation of different proteins and non-protein antioxidants in response to increasing of non-physiological quantities of oxidative agents.

During lipid peroxidation processes are formed many non-long living reactive agents, which accidentally combine with cellular substances. The lipid peroxidation has apparently a dramatic influence on physiological and biochemical processes in the living systems. In response to changes of the cell membrane structures many physiological/biochemical responses and also gene expression can be initiated. In this connection the next question arises: Are changes in the cell membrane structures really involved in the generation of signaling molecules? At first sight lipid peroxidation products might serve as first signaling molecules. In fact, very large

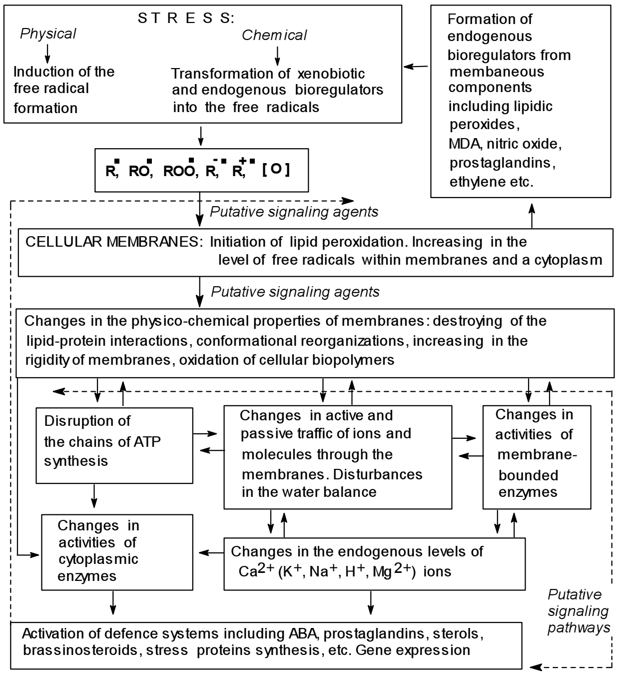

Fig. 2. Formation of putative signaling pathways in the cell during oxidative stress. All free radical species can induce diverse signaling pathways which can lead to genomic or non-genomic responses.

quantities of reactive and non-reactive substances are formed during oxidative outburst. In this connection it is necessarily to distinguish between the chemicals that further initiate new chemical processes and the chemicals that are end products of oxidative reactions.

In the living creatures protective mechanisms exist for the removal of toxic reactive products by substances termed antioxidants. Diverse antioxidant defense systems have evolved mechanisms to enable adaptation to oxidative environments.

Oxidative stress may possibly exert both deleterious and beneficial effects. Lipid peroxides as well as reactive oxygen and nitrogen species may function as regulators of gene expression and mediators of cellular signaling.

We proposed that free radicals and antioxidants including carotene, sterols, brassinosteroids, 1′,4′-diol ABA, prostaglandins such classes as PGF and PGE play a pivotal role in the biochemical pathways which are mediated by lipids of membrane systems. Schematically these processes are presented in Fig. 2 [3].

We believe that formation of these and many others putative signaling molecules may reflect only the final processes of structural ruins in the cell and thus they signal on the destructive events already occurred in the cell.

During oxidative burst can be oxidized HO-groups of serine, threonine and tyrosine that compose membrane and cytosol proteins. Oxidized hydroxy groups of proteins may combine with free radicals of any cellular chemicals including growth regulating substances to form putative biologically active structures (sophistical receptors). In the most cases they present the accidental reactions of free radicals of growth regulating substances with serine, threonine and tyrosine amino acids.

As mentioned above from 20 to 30 % of the proteins encoded in the human genome are membrane proteins which may be implicated in signal transduction [9]. Are the integrity and functional activity of receptors during oxidative stress lost? And if so, by how much?

Cellular signaling in eukaryotes is a complex process in which events that occur within membranes are coordinated with processes that occur in the cytosol. The number of possible reactions that take place in such complex processes is enormous. How this occurs is still not well understood. Moreover, entire membranes do not liberate signaling molecules.

In this connection we believe that from broken or damaged lipid rafts and caveolae of membranes are liberated real signaling molecules that present the short molecules of DNA (see my another paper in this issue). Also they may be termed as receptors or primers.

Conclusion. Current view of the molecular architecture, first of all the plasmalemma, remains poorly understood. In our view, however, the current understanding of the initial molecular mechanism action of the physical and chemical factors on the living systems is also very limited. It is unclear whether growth regulating substances directly bind to nuclear DNA or regulate gene expression by interacting with DNA-binding proteins. The experimental data suggest the growth regulating factors have overlapping yet distinct functions and thus should have different downstream targets.

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Взаємозв'язок між біологічними мембранами і сигнальними посередниками. I. Як це можна пояснити?

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Резюме. Розглянуто значення структури мембран відносно біологічних сигнальних систем відповідно до сучасних знань, а також особливості біологічних мембран і функції, які вони виконують у живих системах. Описано, як сполучаються між собою жирні кислоти в мембранному шарі ліпідів. Дискусійні дані дібрано відносно досягнень молекулярної організації мембран та їхньої ролі в сприйнятті сигналів, трансформації і доставку їх до мішені й шляхами у відповідь. Однією з важливих загадок відносно механізму сприйняття залишається те, як ці процеси співвідносяться з геномними і негеномними відповідями.

Ключові слова: ліпіди, мембрани, оксиданти, рецептори, сигнальність.

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