ISSN 1070-3632, Russian Journal of General Chemistry, 2012, Vol. 82, No. 3, pp. 554–563. © Pleiades Publishing, Ltd., 2012.
Original Russian Text © V.N. Borshch, E.R. Andreeva, S.G. Kuz'min, I.N. Vozovikov, 2010, published in Rossiiskii Khimicheskii Zhurnal, 2010, Vol. 54, No. 6, pp. 78–86.

New Medicines and Approaches to Treatment of Atherosclerosis

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Received November 12, 2010

Abstract—Prerequisites for the use of photodynamic therapy (PDT) to treatment of atherosclerosis, as well as the development and structure of atherosclerotic vascular lesions in humans are analyzed. The basic requirements for PDT components, specifically photosensitizers (PS), and the radiation source, and the current state of their development are overviewed. Some original results of *in vitro* studies of the effect of PS on the basis of phthalocyanines and radiation on cells from the atherosclerotic plaques are presented.

DOI: 10.1134/S1070363212030346

INTRODUCTION

Cardiovascular diseases underlain by large-vessel atherosclerosis are the main cause of deaths in Russia and other economically developed countries. Atherosclerotic lesions of human blood vessels (plaques) form the morphological basis for the development of such cardiovascular diseases, as ischemic heart disease and heart and brain attacks.

Over the past decades impressive success has been achieved in the development of medicines for cardiovascular diseases. However, such treatment still remains largely symptomatic, not intervening into cell mechanisms of atherosclerotic lesions in blood vessels. Synthesis of medicines which would act at the level of vascular walls to prevent the development of atherosclerotic lesions or induce their regression has been the subject of numerous research works. However, to create medicines targeted directly to affected cells still remains quite an urgent task.

One of the most promising methods of treatment for atherosclerosis, based on the action on vascular walls, is photodynamic (PD) therapy. Photodynamic therapy is a two-component method of treatment. One of the components is a photosensitizer: a drug (as a rule, a coloring agent) which acts on biological tissues; the other component is a low-intensity monochromatic radiation with a wavelength corresponding to the absorption band of the photosensitizer.

Photosensitizers are capable of being accumulated and staying for a long time in fast proliferating (i.e. fast growing) cells and tissues. Exposure of a photosensitizer to light initiates a photochemical reaction generating singlet oxygen which is the main destructive factor damaging and killing cells which have accumulated the photosensitizer. The death of cells and their fragments induces natural tissue reparation, a process that removes the destroyed cell material and triggers a natural biological mechanism involving consecutive phases of the inflammation process, specifically infiltration (elimination) and reparation (substitution), and forming a connective tissue cicatrix.

Photodynamic therapy has been first suggested and found wide application in treatment of tumor diseases [1, 2]). Later PD therapy was used to treat other diseases, such as endometriosis, psoriasis, fibrocellular hyperplasia of endothelial vessels, and rheumatic and psoriatic arthritis [3–16]. Photodynamic therapy holds great promise in ophthalmology [13, 17–20] and for suppression of pathogenic microflora [2, 21–23].

Recent animal experiments provided ample evidence for successful use of PD therapy for preventing or

reducing the intimal hyperplasia, i.e. thickening of the innermost layer of a blood vessel (intima). It was shown that photosensitizers affect both directly cells in the intimal thickening [24–26] and the extracellular matrix (connective tissue) [24, 27, 28]. According to preliminary data, the PD method may prove useful for preventing and treating atherosclerotic lesions in vascular walls. The results of model experiments allow us to expect successful PD therapy of vascular pathologies in humans.

Development and Structure of Atherosclerotic Lesions in Human Blood Vessels

According to recent model experimental data, the development of atherosclerotic lesions of blood vessels is initiated when lipids, particularly cholesterol, embed in the arterial wall. This process is accompanied by the accumulation of macrophages–cells circulating in blood. One of the functions of macrophages is lipid phagocytosis (dissolution). Macrophages, in their turn, transmit to smooth muscle cells which start to proliferate and finally block the blood vessel. This is an oversimplified scheme of the process. It should also be taken into account that the biology of human cells differs from that in animals.

At present the cell biology of the vascular wall is one of the main lines of research into the formation and development of atherosclerotic lesions of human blood vessels (see, for example, [29–34]). Modern views on the cellular composition of the vascular wall in sites unaffected and affected by atherosclerosis are based on histological, electron microscopical, and immunocytochemical data. In the intimal arterial layer which is directly involved in atherogenesis (atherosclerotic vascular damage), smooth muscle cells, macrophages, lymphocytes, as well as mast and pericyte-like cells were found.

Thus, the morphological basis of atherosclerotic damage of human cells is a result of complex interacttion of different types of cells, both circulating in the blood stream (monocytes and macrophages, lymphocytes, mast cells, etc.) and forming the structure of the vascular wall (endothelium, smooth muscle cells, fibroblasts, pericytes–poorly differentiated cellular elements of the vascular wall). On PD therapy all these cells will be affected.

There are no definite target cells for PD exposure, since, depending on the phase of atherosclerosis, the same cells can fulfill different functions. Thus, for example, macrophages entering the lipid accumulation site and phagocytizing these lipids, function as cleaners. But the same macrophages, by isolating enzymes which destroy the connective tissue matrix, thin the plaque cap and make it susceptible to rupture which may entail clinically significant complication. Smooth muscle cells which form the basis of the cellular population of a vessel, impart tone and elasticity to the vascular wall. However, the accumulation of lipids in the same smooth muscle cells in atherosclerotically affected vessels may enlarge lesions and render them weaker.

On the other hand, in the case of atherosclerotic lesions, unlike tumors, the therapy is not targeted at complete elimination of one or another type of cells. Here to retard the process, for example, to attenuate enhancement of the fagocytic activity of macrophages or proliferative activity of smooth muscle cells.

The heterogeneity of the cellular population of vascular walls calls for research into adaptation of available photosensitizers to components of the atherosclerotic plaque. Search for new generation photosensitizers for treatment of vascular pathologies should be continued.

Components of Photodynamic Therapy, Their Interrelation, and Principal Requirements to Them

The efficiency of PD therapy depends on the properties of both its components: photosensitizer and source of monochromatic radiation, and, therewith, the first component plays here a leading role. The requirements of photosensitizers [35, 36] include, as an obligatory requirement, ability to absorb long-wave visible light ($630 < \lambda < 800$ nm) with a high extinction coefficient and a high yield of long-lived triplet states. Radiation in this wavelength range is able to deeper penetrate scattering media, including biological tissues. The upper limit of the wavelength range is determined by the excitation energy of the triplet state of the photosensitizer molecule, which should be enough for the triplet−singlet transition (the excitation energy to the lowest singlet state of O_2 is 0.98 eV, which corresponds to the wavelength 1270 nm [37]). Strong absorption at this band makes it possible to decrease the required radiation dose for minimize side effects, which, together with the high yield of the triplet state of photosensitizer, makes it possible to decrease the therapeutic dose of the latter.

One more obligatory requirement is a low dark toxicity of photosensitizer in therapeutic doses.

Furthermore, of importance is the rate of its accumulation in tissues and excretion from the body: The desirable elimination half-life is about a day. If the biological half-life of the photosensitizer is too long, the patient should avoid exposure to direct sunlight to prevent skin and eye lesions.

On too intense radiation partial or even complete destruction of the photosensitizer molecule may occur. The active particles formed on such destruction can cause a shift or even disappearance of the target absorption band, i.e. photobleaching [38, 39]. This process, provided it occurs when the absorbed doses are higher than therapeutic, plays a positive role, protecting the surrounding tissues from overdosing.

The other requirements to the photosensitizing molecule are as follows: high degree of purity, reproducible composition (especially for photosensitizers obtained from natural raw materials), stability on storage, solubility in water, and lack of association of photosensitizer molecules on adsorption on biological tissues, since this adversely affects their photophysical and photochemical properties. The production technology should guarantee an acceptable cost of photosensitizers.

As to the radiation source, it should generate an intense and readily controllable light beam with a sufficiently narrow frequency band (to decrease the risk of side effects). Such sources are lasers (most commonly semiconductor) and, less common, light diodes or white light sources with filters [40]. The light beam can be delivered to the action site from the outside through skin (in the case of superficial blood vessels) or via a light guide introduced directly into the vessel (endovascularly).

Photosensitizers, Their Photophysical and Photochemical Properties, and Distribution in Cells and Tissues

The first photosensitizer found a systematic application in the PD therapy of cancer diseases is a hematoporphyrin derivative (HPD, Photofrin-1), a product of hemoglobin metabolism [41]. However, during clinical use this product showed a number of serious drawbacks, namely, a long biological half-life (several weeks), insufficient accumulation in tumors, short absorption wavelength (630 nm), as well as difficult isolation of individual components (the hematoporphirin derivative is a mixture of monomeric and polymeric porphyrins) [42–45]. Therefore, research into the development of more advanced photosensitizers of the next generation was initiated.

The structures of some photosensitizers passed clinical trials and suggested for use are shown in Fig. 1 [46–51].

Structurally, many photosensitizers are based on the porphyrin (cyclic pyrrole) system contained in the chlorophyll and bacteriochlorophyll hemes. The spectra of porphyrins have a strong absorption band about 400 nm (Soret band) and a series of weaker long-wave absorption bands (*Q*-bands). The longest wave porphyrin absorption band (630 nm) is very weak.

More promising are tetrapyrroles containing one (chlorins) or two (bacteriochlorins) pyrrole rings with reduced double bonds. The target absorption band of chlorins falls in the range 650–690 nm, whereas that of bacteriochlorins has a longer wavelength and is even stronger. Research on various derivatives of chlorine and bacteriochlorin is in progress.

One more class of photosensitizers is formed by phthalocyanine or naphthalocyanine derivatives which show a strong absorption band at $\lambda > 650$ nm. Since phthalocyanines in themselves are scarcely soluble in water, their soluble derivatives, most frequently sulfonated, are used [50, 51].

Only those metal complexes with porphyrins and phthalocyanines (a broad class of biologically active substances) that have diamagnetic metals in the inner coordination sphere are capable of undergoing high-yield transitions into excited high-spin states (and, consequently, with a high yield of singlet oxygen) [52].

A new class of novel synthetic photosensitizers on the basis of conjugated pyrrole rings is under development, and known natural and synthetic dyes on the basis of other structures have been tried [53–57].

Let us consider a physical picture of excitation of a photosensitizer molecule.

Absorption of a quantum of radiation forms a short-lived (10^{-7}–10^{-9} s) excited singlet state of the photosensitizer molecule, which can be deactivated by three channels. Most excited photosensitizers can return into the ground state by emitting the absorbed light dose (fluorescence). Fluorescent radiation allows one to control the absorbed light dose and identify sites of photosensitizer localization. The excitation energy can be quenched by intersystem crossing (energy−heat transition). The target channel is a radiative intercom-

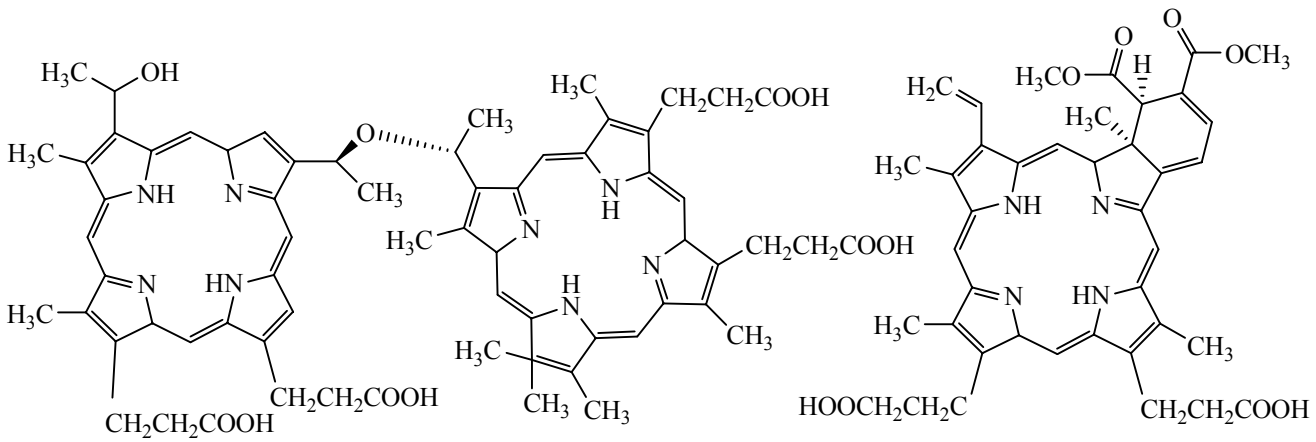
bination transition into the first excited triplet state whose return into the ground singlet state by radiation (phosphorescence) is spin-forbidden. Therefore, the lifetime of the first triplet state is much longer (for typical photosensitizer molecules, about 10^{-3} s). The excitation energy of this state can be quenched by interaction with the oxygen molecule (triplet-triplet interaction), which will form an excited oxygen molecule in the singlet state. This is a direct-action reagent, since singlet oxygen is a strong oxidant, but it has a short lifetime, and, therefore, its action radius is not too long (on average, about 20 nm [58]). Consequently, to be the most effective, photosensitizers are better to be adsorbed on cell or tissue surfaces.

Furthermore, electron transfer from excited photosensitizer to oxygen to form the superoxide anion O_2^- which can produce hydrogen peroxide by the following reactions [59–61]:

$$O_2^- + H^+ \rightarrow HO_2;\ HO_2 + O_2^- (+ H^+) \rightarrow H_2O_2 + O_2,$$

$$HO_2 + HO_2 \rightarrow H_2O_2 + O_2.$$

Hydrogen peroxide takes part, in small amounts, in cell metabolism and, therefore, is present in body



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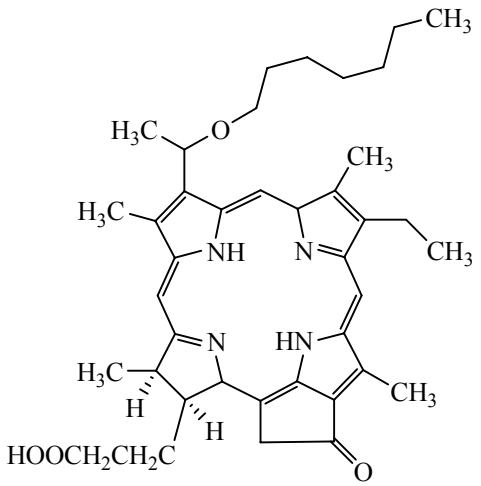

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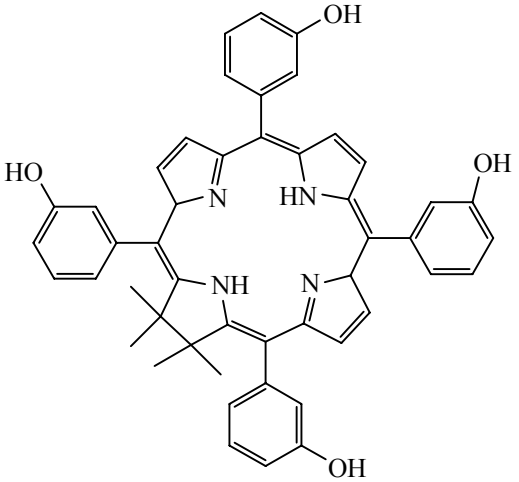
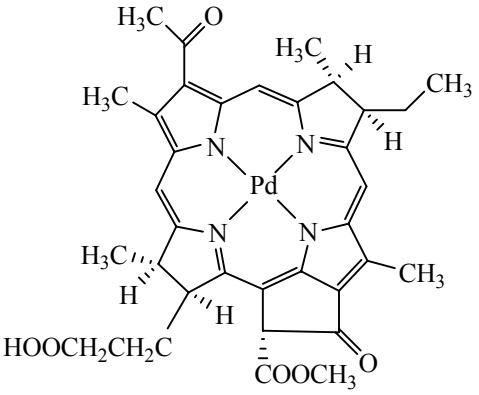


IV

Fig. 1. Structural formulas of photosensitizers: (**I**) hematoporhyrin derivative (HPD, Photofrin-1); (**II**) benzoporphyrin derivative (BPDMA, Verteporfin); (**III**) pyropheophorbide-*a* hexyl ester (HPPH); (**IV**) *m*-tetra(hydroxyphenyl)chlorin (foskan); (**V**) palladium bacteriochlorin (Tukad); (**VI**) silicon phthalocyanine (PC4); (**VII**) indium pyropheophorbide (MV6401); and (**VIII**) sodium salt of sulfonated hydroxyaluminophthalocyanine (Photosens).

Fig. 1. (Contd.)



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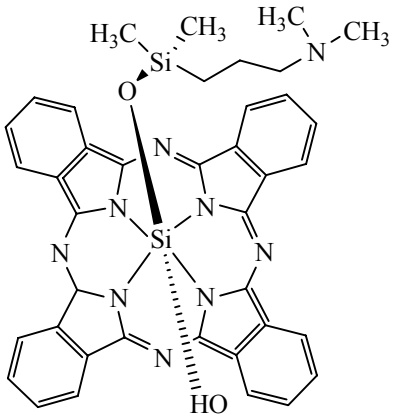

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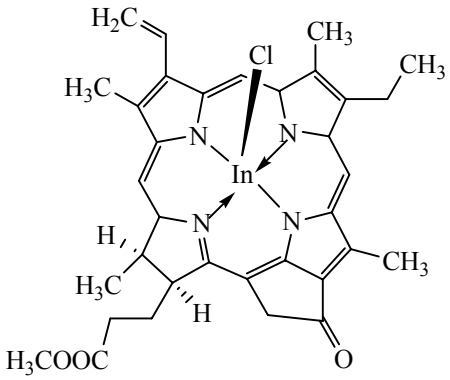

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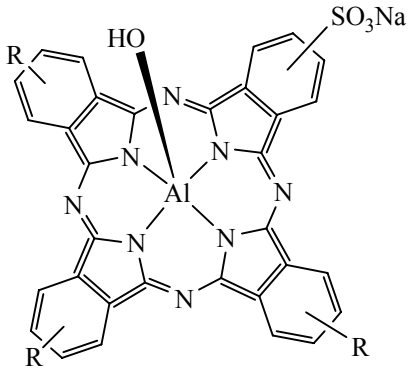


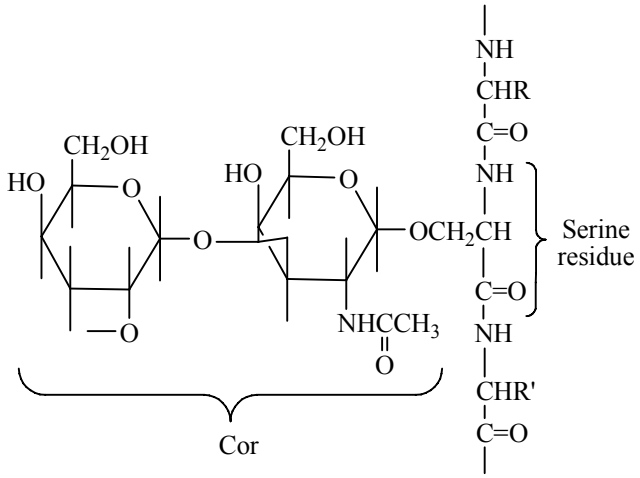
R = H or SO_3Na

tissues. By the Fenton reaction involving iron ions, H_2O_2 can decompose into the hydroxyl radical •OH and hydroxide ion. The $^{\bullet}$OH radical is also generated by the reaction of singlet oxygen with hydroxide ion. Hydrogen peroxide and $^{\bullet}$OH can pass through cellular membranes. The $^{\bullet}$OH radical, togenter with molecular oxygen, takes part in radical oxidation of biological structures [49]. One more effective oxidant is peroxonitrite $OONO^-$ formed by the reaction of the peroxide ion with a molecule of NO which controls contraction of the vascular wall.

Of importance is the distribution of photosensitizers on their adsorption on various biological tissues, since in this case, as already noted, they will most effectively act on tissues. The structure of a concrete photosensitizer not only predetermines its photophysical and photochemical properties, but also affects the energy of noncovalent (hydrogen and van der Waals) bonds with functional groups characteristic of cell surface structures (glycocalix), cellular membranes (primarily of the lipid type), as well as for matrix components: fibers (collagen, elastin), etc. The energy of these bonds controls preferential adsorption of photosensitizers, i.e. their distribution in different parts of the atherosclerotic plaque. Unlike the distribution between organs (for example, see [62]), the distribution of photosensitizers of various structure inside organs, not saying about lumps, have been much poorer studied. This issue could be approached, at least at a quantitative level, by means of quantum-chemical analysis of the interaction of photosensitizer molecules or their fragments with models of surfaces of various biological tissues. Note that over the past time the numbers of published theoretical works on both porphyrin and phthalocyanine photosensitizers has increased (see, for example, [63–70]), but these works are focused primarily on photophysical and photochemical properties and do not touch upon interaction of photosensitizers with biological tissues.

We calculated the electron density distributions in a molecule of porphyrin, as the simplest model of the nucleus of many photosensitizers, with its geometry optimization both in the ground (singlet) and excited (triplet) states. The calculations were performed by the density functional method with a B3PW91 functional, using the Firefly open source media server (PC GAMESS) [71]. According to the calculations, the central part of the porphyrin molecule both in the ground and excited, triplet states is charged negatively, whereas the outer part is charged positively, and this polarization is enhanced by excitation. Consequently, unsubstituted porphyrin molecules will be adsorbed, by their central part, mostly on electropositive groups of substrates or on groups capable of forming hydrogen bonds with NH groups, whereas their outer part will be preferentially adsorbed on electronegative groups. The spin density in a triplet porphyrin molecule is mostly localized on carbon atoms bridging the pyrrole rings. Here interaction with oxygen molecules is possible, followed by excitation. Furthermore, as follows from the calculations, the singlet−triplet transition slightly strengthens both C−N and most C−C bonds.

Subsequent analysis of specific adsorption of the photosensitizer on different parts of atherosclerotic formations (cells, connective tissue matrix, etc.). The outer part (overmembrane structure) in cells incorporated into atherosclerotic plaques, like in cells at all, is formed by glycocalix, a glycoprotein complex responsible for cell interaction with extracellular environment and neighboring cells. The overwhelming part of glycoproteins (protein polypeptide chains associated with oligo- or heterosaccharide chains) is built by the following blocks:



The protein serine residue can be substituted by a methionine residue. The saccharide chains include *N*-acetylglucosamine, *L*-fucose, and/or *N*-acetylneuraminic acid. To a first approximation, the model of the glycocalix surface is a complex of six-membered rings covered with OH groups. Photosensitizers containing in the side chains oxo, hydroxy, and carboxy groups (and other acid residues) will be primarily adsorbed on the core. Water-soluble porphyrin photosensitizers with few substituents will, as mentioned above, will be adsorbed on the core with the participation of NH (and partly N) groups, but related compounds with a lot of substituents are much stronger adsorbed.

Further component of atherosclerotic formations, i.e. the extracellular matrix, is formed largely by collagen and elastin fibers. The structural units of the collagen fiber are fibrils: oblong molecules of tropocollagen. This protein consists by 1/3 of glycine residues and by 1/3 of proline and 4-hhydroxyproline residues.

Vascular collagen is especially rich in glycine and hydroxyproline. The concentration of OH groups on the surface of collagen fibers is low and, moreover, they are involved in bonding of the three intercoiled individual collagen fibers. Therefore, the best available groups for binding with photosensitizers will be the OC–NH peptide groups which can bind exclusively with core –N and –NH centers of photosensitizer molecules, but these bonds are weaker than with core OH groups of glycoproteins.

Unlike collagen, the primary protein structure of elastin features a low content of polar amino acid residues. Elastin mostly consists of nonpolar desmosine and isodesmosine residues built on the basis a substituted pyridine molecule of four lysine residues from different peptide chains. Substituted photosensitizers can be adsorbed on elastin exclusively by nonpolar substituents, whereas unsubstituted photosensitizers, exclusively by the outer part of the molecule. Such bonds are classed with dispersion π−π bonds (see, for example, the review [72]), and they have much lower energies. Therefore, direct adsorption of even highly substituted porphyrin photosensitizers on elastin is ineffective.

Andreeva and co-workers [73–83] performed an *in vitro* study of accumulation in and release from cells and tissues present in atherosclerotic plaques, as well as cell death rates as a function of the accumulated substance quantity. The effect of Photosens and its

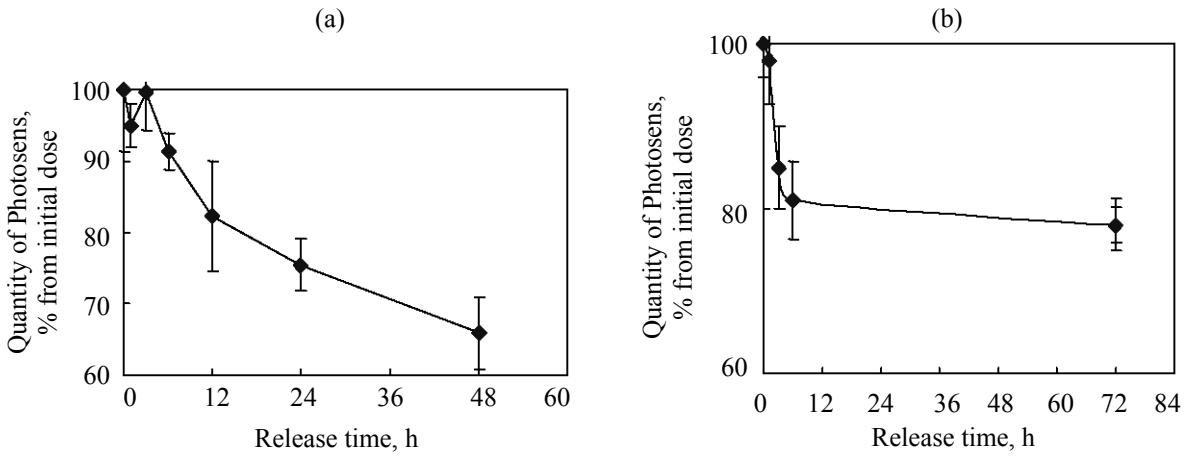


Fig. 2. Kinetic curves of Photosens release from (a) endothelial cells and (b) macrophages of peripheral human blood after 24-h incubation.

metal-free analog Alasens on human peripheral blood monocyte-derived macrophage and human umbilical vein endothelial cell cultures was studied. The highest accumulated photosensitizer quantity was found after 24-h incubation at photosensitizer concentrations of up to 10 μg ml^{-1}, whereas higher concentrations proved to be toxic for both cell types. The viability of cells accumulated photosensitizers decreased almost linearly with accumulated radiation dose.

It was shown that even though the concentration of photosensitizers in macrophages was much higher (2.3 μg mg^{-1} protein) than in endothelial cells (0.3 μg mg^{-1} protein), the 80% lethal radiation doses LD_{80} for macrophages are much higher (20 J cm^{-2}) than for endothelial cells (2 J cm^{-2}). Apparently, macrophages possess a mechanism of antioxidant protection. At low radiation doses (1–2 J cm^{-2}) endothelial cells die via apoptosis, when no inflammation lesions of vascular walls develop. At higher radiation doses endothelial cells die largely via necrosis. Low radiation doses do not affect the viability of peripheral blood macrophages. These cells also show specific photosensitizer release kinetics (Fig. 2).

The low quantity of photosensitizer accumulated in endothelial cells corresponds to its faster and more complete release, whereas with peripheral blood macrophage cells, after the initial fast photosensitizer accumulation stage, stabilization of photosensitizer content at a level of 80% from initial is observed. However, the rate of Photosens release from both types of cells does not fit the modern requirements to effective photosensitizing agents.

Radiation Modes and Sources in Photodynamic Therapy

Not an unimportant condition for a success of PD therapy of various pathologies is that the radiation regime is adequate for a given tissue or organ. In the framework of vascular therapy an active search for optimal parameters of radiation exposure for minimizing side effect is being conducted. In first *in vivo* experiments intense radiation caused enhancement of intimal hyperplasia and irreversible changes, whereas low radiation doses prevented intimal hyperplasia. Some information on dose-dependent effects of low radiation doses is available [84]. The above-mentioned photobleaching effect makes necessary optimization of the level of radiation exposure and fractionation of the radiation dose. Comaring external and internal (endovascular) radiation modes revealed no essential differences [85].

When choosing radiation parameters, one should bear in mind that increased wavelength results in quite a deeper penetration of radiation into tissues and prevents intimal hyperlasia. Adverse effects are associated exclusively with intense radiation. Furthermore, it seems possible to choose optimal parameter of laser radiation, which would exclude the risk of plaque detachment and vascular wall damage, due to resonance interaction with the microstructure of atherosclerotic plaques [86]. An analogous resonance effect is observed, for example, on exposure of kidney stones to modulated laser radiation. This is explained by the fact that any isolated structure has certain specific energy dissipation frequencies which depend on the physical

parameters of the substance (density, thermal conductivity, characteristic structure size, etc.). For structurally complicated biological objects one is able no more than to estimate the frequency range and then to find optimal radiation parameters by experimentation.

Endovascular irradiation requires a low radiation dose for preventing damage of blood corpuscles. The required results can be reached by means of the resonance pulse-periodic regime of modulated radiation and intrapulse modulation of laser radiation power [85, 86]. To this end, sources with such controlled parameters as pulse rise rate and on−off ratio, as well as intrapulse amplitude modulation of radiation power and variability of pulse frequency.

In our research the most convenient source of continuous monochromatic radiation in the red spectral region were found to be semiconductor lasers with generated radiation wavelengths of 635, 662, 670, and 690 nm.

The propagation of light beam through an inhomogeneous medium is determined by dissipation and absorption processes. Dissipation depends on the degree of heterogeneity of the medium and occurs largely at interfaces. Absorption is much affected by chromophoric (heme) groups in various proteins (hemoglobine, myoglobine, and cytochrome). The so-called transparency window of biological tissues is 600−1300 nm [49]. The lower extreme is determined by the upper absorption boundary of oxidized and reduced hemoglobin and melanine, whereas upper extreme, by the lower absorption boundary of water molecules.

In PD therapy the so-called self-shielding effect, specifically absorption of radiation by tissues with accumulated photosensitizer, is possible. In this case, radiation affects only those tissues which are adjacent to the light beam. This problem, as mentioned above, can be solved by using photosensitizers sensitive to photobleaching.

CONCLUSIONS

The PD therapy of human vascular atherosclerosis is a promising approach to treatment of this widespread disease. The first results are already encouraging, but a number of still unsolved problems prevent a wide application of this method. New photosensitizers with an optimal complex of properties have to be developed and tested both *in vitro* and in clinical conditions. High-variability radiation sources which would allow widely varying the radiation mode and exactly controlling the radiation dose are still to be developed. Even though the PD therapies of tumors and atherosclerosis have much in common, in the case latter case there is no rigid requirement to kill all damaged cells. On the other hand, in developing the strategy of treatment one should tend to attenuated exposure regimes so that not to induce heavy inflammations which would entail secondary degeneration of vascular walls. Therefore, newly developed photosensitizers should be effective at low radiation doses leading primarily to apoptosis of the cellular population of atherosclerotic plaques.

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