SERUM ALBUMIN AS A SOURCE OF AND A TARGET FOR FREE RADICALS IN PATHOLOGY

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Oxidative stress caused by excessive accumulation of pro-oxidants and/or depletion of antioxidants, is an important pathogenic factor. Oxidative stress leads to oxidative modification of macromolecules. Proteins are a target for oxidizing agents. Of other antioxidants in human blood plasma, serum albumin is particularly interesting as a target for reactive oxygen species. In this brief review albumin is looked upon as a target for free radicals, an antioxidant, and a source of free radicals in its complexes with copper ions. Possible targets for free radicals in protein structure and the consequences of their exposure to free radicals attacks have been analyzed. The role of glycosylation in contributing to protein oxidative modification has been studied. The original experimental data on albumin structure changes in various models of oxidative stress obtained by a spectrofluorimetric method are pesented. Increased antioxidant properties of albumin modified in a physical model of oxidative stress (UV-irradiation) have been described.

Keywords: oxidative stress, free radicals, human serum albumin

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СЫВОРОТОЧНЫЙ АЛЬБУМИН КАК ИСТОЧНИК И МИШЕНЬ СВОБОДНЫХ РАДИКАЛОВ В ПАТОЛОГИИ

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Окислительный стресс, вызванный избыточным накоплением прооксидантов и/или истощением антиоксидантов, является важным патогенетическим фактором. Он вызывает окислительную модификацию макромолекул, и одной из мишеней окислителей являются белки. Среди антиоксидантов в плазме крови человека особый интерес в качестве мишени для активных форм кислорода представляет сывороточный альбумин. В нашем кратком обзоре он рассмотрен как мишень для свободных радикалов и антиоксидант, а также как источник свободных радикалов в комплексе с ионами меди. Проанализированы возможные мишени свободных радикалов в структуре белка и последствия воздействия радикалов на них. Уделено внимание роли гликозилирования как одного из факторов, способствующих окислительной модификации белков. Приведены собственные экспериментальные данные об изменениях в структуре альбумина при разных моделях окислительного стресса, полученные спектрофлуориметрическим методом, проиллюстрировано усиление антиоксидантных свойств альбумина при физической модели окислительного стресса (ультрафиолетовое облучение).

Ключевые слова: окислительный стресс, свободные радикалы, сывороточный альбумин человека

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Free radicals are an important component of cellular metabolism. They induce a number of negative effects if accumulated in excess, including the structural and functional damage of the cell and even its death through necrosis or apoptosis. A shift in balance between free radicals (pro-oxidants) and antioxidants in favor of the former is called oxidative stress (OS). Various factors cause OS, but all of them eventually lead to the oxidative modifications of macromolecules, such as DNA or proteins, and to lipid peroxidation. A new research area has emerged, namely, research of protein oxidative modification (POM) [1]. The knowledge accumulated in this area is not only of fundamental significance, but also is widely applied in actual practice. Recently, tests detecting oxidized proteins in blood cells and tissues have been introduced, making it possible to collect extensive factual material. POM has been found to induce formation of tyrosine and tryptophan oxidation products,

including *o*- and *m*-tyrosines, 3,4-dihydroxyphenylalanine (DOPA), carbonyls and other oxidized derivatives; dimers (dityrosines) are formed; auto-oxidative glycosylation of proteins occurs [2].

A complex antioxidant system of the organism resists free radical oxidation. Blood plasma proteins with antioxidant properties are components of this system [3]. Among them, a key role is assigned to human serum albumin (HSA). This protein interacts with free radicals, undergoes oxidative modification and protects the body. Albumin oxidative modification causes complete or partial loss of its diverse functional activity, which in itself can produce a variety of effects. However, during this process HSA acquires new properties and, possibly, new functions. Besides, albumin modified by oxidation can be an effective marker of OS.

Considering the increased interest in HSA role in free radical oxidation, we thought it important to summarize all the data collected and to examine this protein from two perspectives: as a source of and as a target for free radicals.

Serum albumin as a source of free radicals

In blood plasma there are two main proteins responsible for copper binding and transportation that at the same time prevent copper damaging effect on other plasma proteins, blood cells and surrounding tissues [4]. Ceruloplasmin contains copper in its active site. Reactions involving this protein are not accompanied by the formation of any radicals. The second largest copper pool in blood plasma is associated with human serum albumin that contains a high affinity site for copper, namely, the N-terminal tripeptide Asp-Ala-His (Cu^{2+}/Ni^{2+}-binding motif) [5]. Under normal conditions less than 1% of total albumin is copper-bound, but this amount is enough to generate a big number of radicals in blood. In some pathological states, for example, Wilson's disease or arthritis, the level of albumin bound copper can be considerably higher (2 to 5 times)[6–8].

Y.A. Gryzunov et al. [9] thoroughly investigated the conditions and reasons related to the change in the radical producing (pro-oxidant) activity of HSA-copper ions complex. Those authors studied, firstly, the effect of cystein-34 amino acid residue (Cys-34) modification on catalytic activity of the complex, and, secondly, the result of non-esterified fatty acid binding to albumin. To monitor the pro-oxidant activity of the complex, the rate of ascorbate radical formation was measured by the electron paramagnetic resonance assay (EPR), since ascorbate is one of the main interceptors of free radicals in blood plasma. At copper-albumin ratios below 1:1, the bound copper was almost redox-inactive, as long as Cys-34 was in a reduced state. We will term the inactive complex Cu/HSA-SH. Alkylation, nitrosylation and oxidation of thiol groups induced the catalytic radical producing activity of the Cu/HSA complex. This activity was more than an order of magnitude lower than the activity of free copper ions not bound to albumin. However, the evidence of such activity itself is important. Using ultrafiltration, it was shown that it is the complex with copper:protein stoichiometry of 1:1 and not free copper ions, generated accidentally during Cu/HSA-SH processing, that exhibits such activity.

In that work [9] it was also established that being catalytically inactive, Cu/HSA-SH complex displayed radical producing activity as a result of protein conformational changes when bound to free fatty acids, given that albumin did not contain any fatty acid impurities. Both conformational changes measured by probe fluorescence (fig.1, probes I and II) and catalytic activity reached their maximum at a fatty acid to protein molar ratio of 3:1 for oleic acid and 2:1 for linoleic acid. Parallel to fatty acids binding and profound conformational changes caused by this process, oxidation of Cys-34 SH-groups and a simultaneous increase in redox activity of copper-albumin complex were observed. The authors concluded that fatty acids regulate anti- and pro-oxidant properties of Cu/HSA complex by changing Cys-34 redox status.

The process described above includes the following stages (fig.1):

1) binding of fatty acids in protein domains I, II and III;

2) albumin conformational changes (measured by the fluorescence of probes I and II);

3) activation of catalytic (redox) activity of the Cu complex in the binding site;

4) Cys-34 SH-group oxidation;

5) oxidation of other molecules by dissolved oxygen facilitated by Cu/HSA and accompanied by free radicals formation (oxidative stress).

Thus, pro-oxidant properties of HSA complex with copper ions are implemented only after protein SH-group has been oxidized or a thiol group has interacted with nitrogen monoxide (NO).

Serum albumin as a target for free radicals

A lot of data confirm that HSA antioxidant activity is determined by at least three factors: 1) its binding of variable valency metals, such as copper; 2) its reactions with free radicals (a radical trap); 3) the formation of products with antioxidant properties during its oxidative modification.

If HSA is added to blood lipoproteins that are quickly oxidized in the presence of copper ions, then lipid peroxidation in lipoproteins is inhibited [10], but not blocked completely, because copper retains its catalytic activity in the complex with albumin. It means that HSA is an antioxidant because it forms a complex with copper ions. However, this complex alone cannot be a pro-oxidant, which depends on the amount of albumin-bound copper in blood plasma and this complex activity. As stated previously, binding of NO and fatty acids, as well as a chemical modification of Cys-34 thiol group, makes Cu/HSA complex catalytically active. In contrast, native HSA completely inhibits catalytic activity of copper ions.

In serum albumin, Cys-34 SH-group is a primary radical interceptor; because of this group HSA constitutes the majority of reactive thiols in blood plasma [11, 12]. Cys-34 oxidation results in the formation of sulfenic acid (RSOH) that is later oxidized to sulfinic (RSO_2H) or sulfonic (RSO_3H) acids [13]. As mentioned before, SH-groups serve as a defense mechanism against free radical oxidation [14, 15], their concentration in blood plasma lowers considerably when OS increases, which occurs in various diseases [16–18] and aging [19]. Using high performance liquid chromatography (HPLC) with fluorescence detection, K. Oettl et al. studied HSA redox state as a potential systemic marker of OS in patients with various diseases (cataract, glaucoma, age related macular degeneration, diabetes mellitus, diabetic retinopathy and hypertension), with or without complications and with consideration of possible effects on age [20].

Another amino acid sensitive to free radical attacks is methionine. HSA contains 6 methionine residues. Its oxidation by various oxidizing agents leads to the formation of methionine sulfoxide (MetSO). However, changes in HSA properties induced by free radicals are tricky to interpret. To look at enzymes from this perspective, one can refer to the work of R. Levine et al. [21], who found that preferential oxidation of unprotected methionine residues of enzymes had little effect

on the biological functions of glutamine synthetase. At the same time a supposition was made that methionine residues redox cycle in biological systems can be a factor of defense against reactive oxygen species and prevent other functionally important changes in protein structure.

In serum albumin, aromatic amino acids are a third target for free radicals; they can be susceptible to oxidative modification under oxidative stress. HSA consists of 18 tyrosine residues and 1 tryptophan residue. The result of oxidative modification of free tyrosine, tryptophan and albumin is the augmentation of protein protective properties due to the formation of oxidation products that are antioxidants [22]. One of such compounds is DOPA [22].

Thus, attacked by free radicals, HSA loses its free cysteine thiol group, some of tyrosine groups and a tryptophane residue. The higher is the level of OS in human blood (systemic OS in other terms), the higher is the degree of thiol and aromatic amino acid loss. Both of these criteria are currently used for evaluation of OS levels in clinical practice. It is important to note that aromatic amino acids, which are constituents of HSA, are natural fluorophores and their oxidative damage can be measured by a simple and sensitive method of ultraviolet fluorescence registration. This subject was looked upon in a number of studies. Reduced HSA fluorescence was observed when studying the effect of glycosylation [23] and free radicals [24] in a diabetes model. Those authors established a clear correlation between protein molecule conformational changes and protein antioxidant properties; a key role of copper ions in implementing albumin pro-oxidant properties was confirmed. Likewise, reduced analytical signal intensity, which is a useful index of amino acid degradation and displays a clear dependence between oxidation and protein conformational restructuring, was observed when studying the effect of an individual hydroxyl radical (•OH) and its combinations with superoxide anion radical (•OH + $•O^{2-}$) on proteins [25]; when studying thiol groups oxidation and elevated fructosamine levels in patients with obstructive sleep apnea [26]; when assessing protein structural changes mediated by peroxynitrite (by tryptophan and cystein oxidation, tyrosine nitration, dityrosine formation, production of 2,4-dinitrophenilhydrazine, carbonyls and molecule fragmentation) [27]; when modeling a "soft" OS, induced by ascorbate, oxygen and trace amounts of metals [28]; finally, when studying a correlation between HSA oxidative modification growth and the severity of hepatic failure characterized by increased carbonyls and Cys-34 oxidation [29].

It has been shown that protein glycosylation leads to its more intense oxidative modification [30]. In the work of J. V. Hunt and S. P. Wolff [30] this fact was illustrated by the example of tryptophan. Moreover, many observations showed that glycosylation and oxidation are closely related to each other: glycosylation both boosts oxidation and is boosted by it. To describe this property, a new term has been introduced, namely, *"glycoxidation"* — glycooxidation, derived from glycosylation + oxidation [31]. F. Monacelli et al. [31] used fluorescence spectroscopy and circular dichroism analysis to study the end products of oxidation and glycosilation and HSA conformational changes after its incubation with ribose, ascorbic acid (AA) and diethylenetriaminepentaacetic acid (DTPA) in various combinations. Ribose was found to induce a considerable increase of pentosidine (a glycosilation marker), with AA and DTPA preventing its accumulation, especially at later incubation stages. Ribose increased oxidation protein products level moderately, while AA inhibited their formation. Besides, in combination with AA ribose contributed to further formation of oxidation products, while DTPA inhibited oxidation protein products formation induced by AA. Using a circular dichroism analysis, F. Monacelli et al. obtained the results proving that AA and DTPA are strong modifiers of α-spiral part of HSA structure while ribose affects protein structure at late incubation stages only.

After studying the relevant literature, we carried out a series of experiments in our laboratory on using HSA as a marker in various OS models. Albumin structural changes were evaluated using spectrofluorometry; albumin antioxidant properties were evaluated by luminol-enhanced chemiluminescence assay (with some modifications) [32]. Solutions of luminol $C_8H_7N_3O_2$ (Sigma-Aldrich, USA, molecular weight of 177.16), HSA (Sigma-Aldrich, molecular weight of 69,000), AAPH (2,2′-Azobis(2-methylpropionamidine) dihydrochloride, Fluka, Germany) were prepared by dissolving weighted amounts of corresponding substances in phosphate buffer solution (KH_2PO_4, reagent grade). A working concentration of N-formyl-methionine-leucine-phenylalanine (a substance used for neutrophil stimulation) by FMLP,Sigma-Aldrich, was obtained by diluting the initial solution with a medium (Hank's solution containing glucose / HEPES). For irradiation, samples with optical density of no less than 0.2 were used to provide the uniform UV absorption throughout the solution volume and to avoid nonlinearity of fluorescence spectra registration. Neutrophils were extracted from the blood of patients with Wegener's granulomatosis (Tareev Clinic of Nephrology, Internal and Occupational diseases). Measurements were done using RF-5301 PC spectrofluorophotometer (SHIMADZU, Japan) and Lum-5773 chemiluminometer (DISoft, Russia) with PowerGraph software; absorption spectra were registered by Specord 200 spectrophotometer (Jena Eng., Germany). Samples were irradiated in Bio-Link crosslinker (Vilber Lourmat, France), which allows irradiation dose control, with effective short wavelength of 254 nm. The following OS models were used: physiochemical (thermally induced decomposition of AAPH), chemical (albumin exposure to superoxide and hydroxyl radicals produced in Co^{2+}/H_2O_2), physical (exposure to different dozes of UV-irradiation), and biological (radical production after phagocytes activation). Data obtained in the experiments are presented in fig. 2. In all our experiments a 100 Mm phosphate bugger solution with pH of 7.4 was used as a medium. Excitation wavelength for fluorescence spectrum registration was 260 nm.

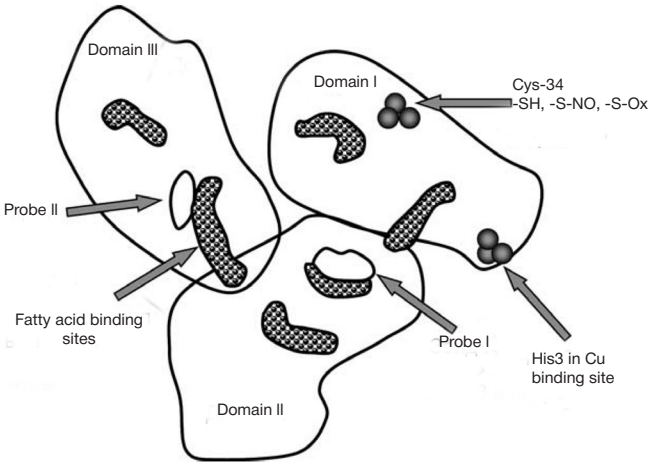

Fig. 1. Location of fatty acid- and Cu-binding sites; location of probes I and II in domains I, II and III in HSA structure

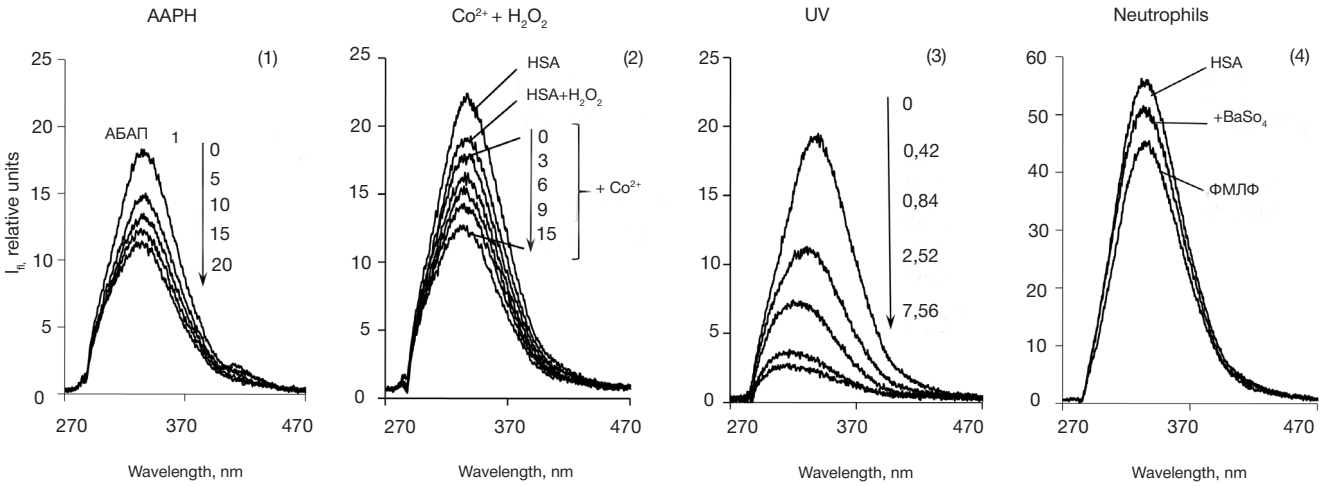

Fig. 2. Fluorescence spectra obtained in the experiments. (1) HSA (0.66 μm) and AAPH (2.5 mM), figures next to curves show incubation time. (2) HSA (0.6 μm), H_2O_2 (3 mM) and Co^{2+} (0.3mM), figures next to HSA + H_2O_2 + Co^{2+} curves show time after introducing Co2+ to the system: 0, 3, 6, 9 and 15 minutes. (3) HSA (0.6 μm), figures next to curves show UV-irradiation dosage, kJ/cm². (4) HSA (fraction isolated from blood plasma and diluted 1:100) combined with neutrophils stimulated by barium sulfate and FMLP

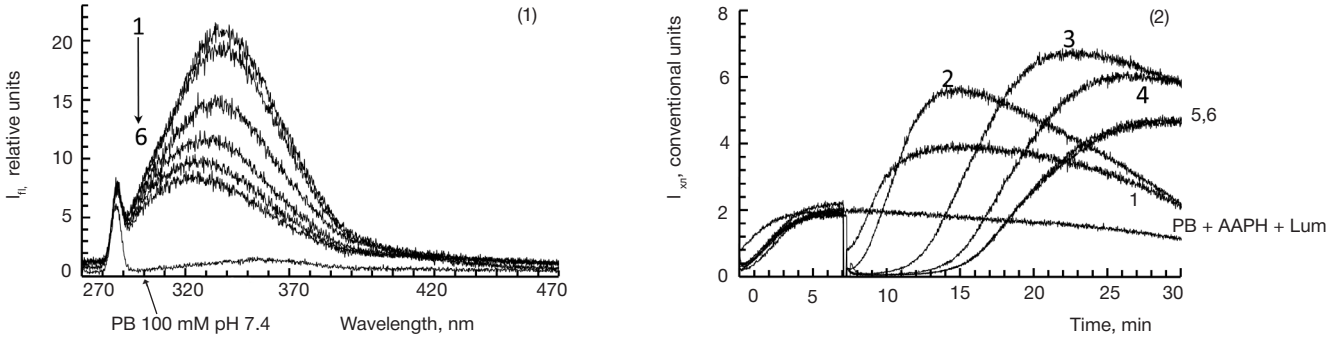

Fig. 3. Changes in fluorescent and antioxidant properties of HSA exposed to different doses of UV-irradiation. (1) HSA fluorescence spectra (0.66 μm); the protein was exposed to different doses of UV-irradiation (figures show the dosage, J/ cm²: 0 — native protein, 1 — 0.050, 2 — 0.200, 3 — 0.400, 4 — 0.600, 5 — 0.800, 6 — 1.000). (2) Chemiluminescence curves of HSA (0.66 μm) exposed to different doses of UV-irradiation (figures next to curves show the dosage, kJ/cm²) in the system containing phosphate buffer solution (PB) (37 °C), AAPH (2.5 mM), luminol (Lum) (2 μm), system total volume 1.000 ml

Study results show that in all OS models protein oxidative modification is observed, which is demonstrated by reduced fluorescence intensity. A physical model of OS (UV radiation) was investigated in greater detail. Experimental data are presented in fig.3. In all experiments 100 Мм phosphate buffer solution with pH of 7.4 was used as a medium; excitation wavelength for registering fluorescence spectra was 260 nm. To register chemiluminescence, the following steps were taken: AAPH and luminal solutions were mixed in a cuvette, the resulting mixture was incubated for 20 minutes at room temperature in the dark, then a phosphate buffer heated up to 37°C in a thermostat was added to the AAPH-luminol mixture. The cuvette was placed in the device, and chemiluminescence was registered until the curve reached the plateau. After the curve displayed a steady level of radical generation, an aliquot of the antioxidant (HSA) was introduced to the system.

Fig. 3 shows a dosage-dependent reduction of analytical signal intensity of the sample exposed to UV, and a simultaneous increase in antioxidant properties of HSA: a “dip” area is growing (latent period, t_{lat} — time during which fluorescence decay is observed below the curve). It can be explained by the fact that products with antioxidant properties are a result of aromatic amino acids oxidation [22]. Fig. 4 shows a correlation between reduced fluorescence intensity and antioxidant activity growth (t_{lat}, min).

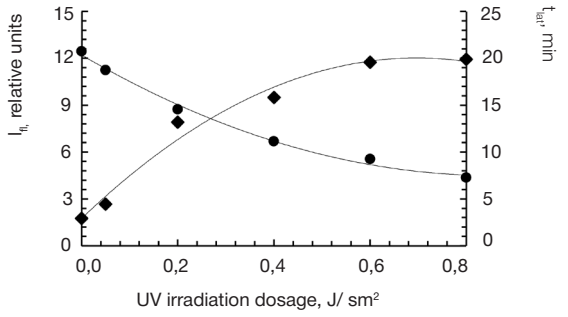

Fig. 4. Comparison of HSA fluorescence changes (0.66 μm) (λ^{340}_{max} = 337 nm) and the increase in the total antioxidant activity (t_{lat}, min) with the increased dosage of short wavelength radiation, J/ cm²

CONCLUSIONS

We have analyzed and summarized known experimental data on albumin being a source of and a target for free radicals. The second largest copper pool in blood plasma is associated with albumin. In different pathological conditions the level of albumin-bound copper increases. The mechanisms and conditions under which pro-oxidant properties of the complex

are implemented were studied. At the same time, albumin itself is the main blood plasma protective protein; it becomes possible because of albumin ability to intercept free radicals. Albumin reveals its protective properties due to the presence of cystein-34 SH-groups. Some contribution is made by 6 residues of another amino acid, namely, methionine, sensitive to oxidation. Finally, aromatic amino acids are responsible for production of substances with prominent antioxidant properties. This fact is supported by our own experimental data. Oxidative modification of serum albumin in various models of oxidative stress was assessed by spectrofluorometry. A physical model (ultraviolet radiation) was studied in more detail: dosage-dependent reduction of analytical signal intensity was demonstrated with the simultaneous increase in antioxidant protein properties that were detected using luminol enhanced chemiluminescence. One of the products of tyrosine oxidation, 3,4-dihydroxyphenylalanine (DOPA), was found to exhibit aintioxidant properties.

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