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Review

ROS-induced lipid transformations without oxygen participation

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ABSTRACT

This review presents data showing the possibility of novel pathways to be realized for free-radical transformations of glycerophospholipids and sphingolipids. These transformations include the stages of formation and subsequent decay of carbon- and nitrogen-centered radicals of the starting lipids resulting in the accumulation of signal molecules. The presence of a hydroxyl group in the polar component of lipids is a prerequisite for the implementation of these processes. This enables their structural modification and/or destruction to take place with the accumulation of biologically active products such as phosphatidic acid, ceramides, diacylglycerols and acylamides.

Sphingolipids containing a free amino group, when interacting with active species of oxygen or chlorine, form aminyl radicals. These lipid radicals undergo further fragmentation, leading to the accumulation of 2-hexadecenal, which has a broad spectrum of biological activity. The presence of an amide group in the structure of sphingolipids determines the possibility of their photodestruction, which also results in the formation of 2-hexadecenal.

In contrast with lipid peroxidation, which is inhibited by reducing agents, free-radical fragmentation reactions of hydroxyl-containing lipids involving carbon-centered radicals are blocked by oxidants.

1. Introduction

A characteristic feature of the oxidative stress, which exerts an important influence on the occurrence of pathophysiological changes in living organisms, is the induction of processes caused by reactive oxygen species (ROS). ROS cause damage to lipids, proteins, nucleic acids and other vital components of biosystems. Among various processes that can generate ROS in biosystems, oxidation reactions occurring in biologically significant molecules were studied the most thoroughly (Davies, 2000; Halliwell and Gutteridge, 2007; Kohen and Nyska, 2002; Sies, 1991). Particular attention was given to investigation of the role and mechanism of lipid peroxidation (LPO) in cell membranes under conditions of normal and pathological functioning of the studied biological objects (Buettner et al., 1993; Frankel, 2005; Porter et al., 1995). This is due to the fact that biomembranes play a key role in the biosystem, whereas lipids and their components are excellent substrates for oxidation.

One may wonder, “Why do the reactions of hydrophobic fatty acid residues with oxygen have such a prominent place in the free-radical biology and medicine?” It is well known that oxygen levels in different organs and cells vary within quite a wide range (Carreau et al., 2011; Semenza, 2012). At low oxygen concentrations, one can hardly expect significant contributions from oxidation processes in the total amount of the reactions taking place. Besides that, most of the ROS are hydrophilic reagents, and some of them, for example ˙OH radicals, are extremely reactive. They tend to react non-selectively forming mostly carbon-centered radicals located in the polar moieties of biomolecules. In a number of cases, such radicals can undergo further transformations before interacting with oxygen.

In our opinion, the exclusive interest toward lipid oxidation processes can be associated with some subjective factors, along with the objective ones. The former ensued from the large-scale studies of free-radical processes in biology, started in the 1950s under the influence of concepts set forth by N. Semyonov and C. Hinshelwood, who won the Nobel Prize in 1956 for the discovery of branching chain free-radical reactions, mostly involving oxygen. A considerable contribution to the development of free-radical biology was made by D. Harman (Harman, 1956) and N. Emmanuel (Emanuel, 1965). Both of them being chemists, they started by studying oxidation processes of hydrocarbons, but later on focused on establishing the role of free-radical oxidation processes as factors associated with aging and the development of various pathologies, including cancer. This situation led to an under-estimation of the

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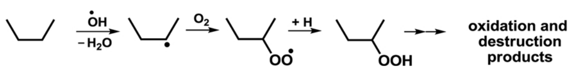
role of other ROS-induced transformations of biomolecules in the functioning of a living organisms.

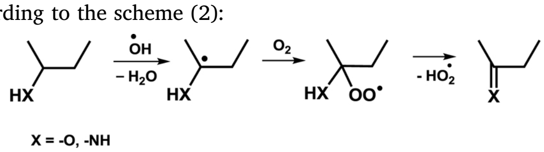
Lipids are known to be amphiphilic compounds containing both non-polar hydrophobic and polar hydrophilic components in their structures (Farooqui et al., 2001; Halliwell and Gutteridge, 2007). Our work carried out over a period of 25 years was focused on ROS-induced reactions taking place in polar components of glycerophospholipids, sphingolipids and the respective modeling compounds for the purpose of assessing the possible role of such processes in essential functions of an organism.

Our studies were based on reliably established experimental results concerning the properties of organic radicals. It is known that the interaction of ROS with bioorganic compounds leads, as a rule, to the formation of carbon-centered radicals from the starting molecules, either by H-atom abstraction or addition to the double bond (Halliwell and Gutteridge, 2007). Further transformations of the C-centered radicals depend on their respective structures. The radicals of alkyl type are consumed mainly in reactions with oxygen forming oxidation products:



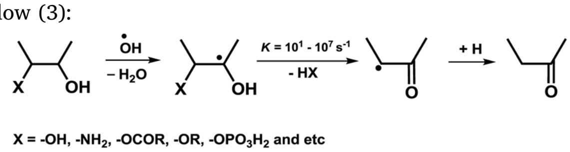
(1)

Monofunctional organic radicals are oxidized with oxygen according to the scheme (2):



(2)

If the structure of an organic molecule contains two functional groups, realization of a fragmentation process is possible, as shown below (3):



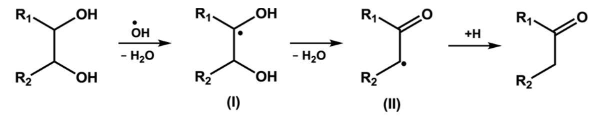
(3)

Reactions of type (3) proceed only in cases when the two functional groups, one of which being an OH group, are located on adjacent carbon atoms. The rate of decomposition of such radicals depends on the nature of X, varying from 10^1 for α-diols to $10^7\, s^{-1}$ for the respective phosphates (Koltzenburg et al., 1976; Samuni and Neta, 1973; Steenken et al., 1974). Reactions of these radicals with oxygen, when it is present at physiological levels, are in many cases too slow to compete with the fragmentation processes, and hence would hardly affect the probability of the radical decomposition.

First, the main features of the fragmentation reactions of bifunctional organic compounds were studied (Petryaev and Shadyro, 1986; Shadyro, 1997). Later on, these processes were investigated on more complex biologically relevant compounds, including carbohydrates (Edimecheva et al., 2005; Shadyro and Kisel, 2007), amino acids and their derivatives (Shadyro et al., 2003a; Sosnovskaya et al., 2009) and nucleosides (Petryaev et al., 1988) as well as lipids (Shadyro et al., 2002a, 2004a). Free-radical transformations of lipids and related compounds are discussed in the present review.

2. Free-radical fragmentation of glycerophospholipids and the respective modeling compounds

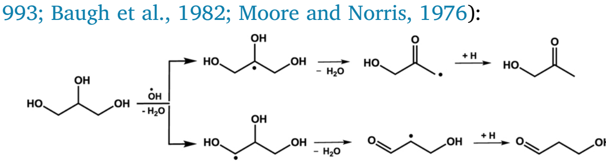
The possibility of decomposition of organic radicals involving rupture of two bonds vicinal to the radical center has been first demonstrated while studying the homolytic transformations of α-diols (Bulley et al., 1966; Gilbert et al., 1972, 1974; Koltzenburg et al., 1976; Petryaev et al., 1978; Petryaev, 1979; Petryaev and Shadyro, 1986; Shadyro, 1997). It has been found that dehydration of α-diols can take place according to a free-radical mechanism as shown in the scheme (4):



(4)

Radicals (I) and (II) were identified by EPR (Bulley et al., 1966; Gilbert et al., 1972; Gilbert et al., 1974). The dehydration rate was shown to depend on the structure of the α-diol, increasing when switching from ethylene glycol to 2,3-butanediol. The fact that the species (I) decomposed significantly faster in acidic media than in neutral ones allowed the authors (Gilbert et al., 1972) to presume that fragmentation of (I) occurred by a heterolytic mechanism. Subsequent detailed studies of the effect of pH on free-radical transformations of α-diols and ethers gave reasons to believe that the radicals (I) may decompose following a concerted pathway via a cyclic transition state, in accordance with the orbital symmetry rules (Petryaev et al., 1978; Petryaev, 1979; Petryaev et al., 1982).

Glycerol, on interaction with radical agents, also dehydrated to yield either hydroxyacetone or propionic aldehyde (Akhrem et al., 1993; Baugh et al., 1982; Moore and Norris, 1976):

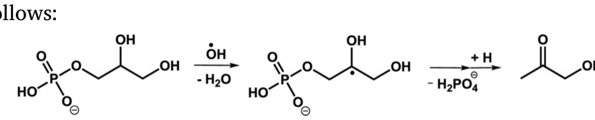


(5)

(6)

The process (5) looks more preferable to (6) because of the higher probability of forming C-2 radicals from the starting molecule.

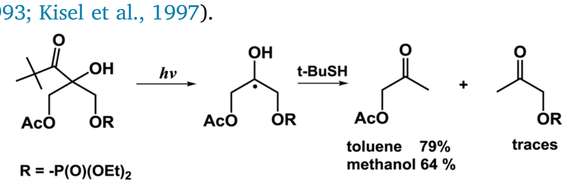
Many studies were focused on the homolytic reactions of glycerol-1-phosphate (Greenstock and Shiermar, 1975; Samuni and Neta, 1973; Schuchmann et al., 1995; Steenken et al., 1974). A characteristic feature of its transformations is dephosphorylation, which proceeds as follows:



(7)

After the radiolysis of aqueous solutions of glycerol-1-phosphate, the yield of the inorganic phosphate was found to be equal to the OH radicals (Greenstock and Shiermar, 1975; Samuni and Neta, 1973). This fact proves high probability of realization of reaction (7) and its high selectivity.

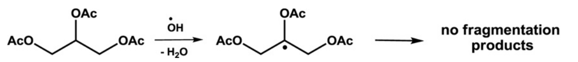
Properties of the glycerol C-2 radicals were investigated in detail by selective generation of these species according to reaction (8) and inducing fragmentation processes in various solvents (Akhrem et al., 1993; Kisel et al., 1997).



(8)

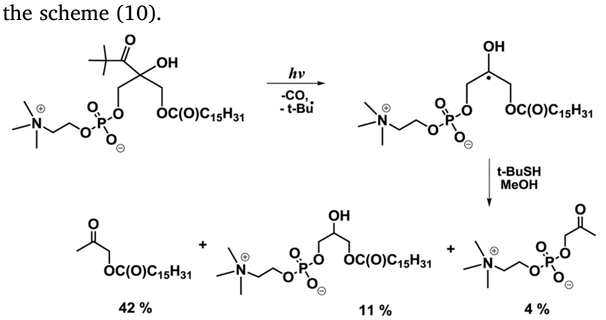
Intermediate and final products of reaction (8) have been identified by EPR and GC–MS. The phosphate elimination rate from C-2 glycerol radicals is greater in toluene than in methanol. This fact is an argument in favor of a concerted mechanism of the decay without involvement of any charged species that should be formed by heterolytic bond cleavage. Substitution of a hydroxy group for the methoxy group in the C-2 glycerol radicals caused blockage of the fragmentation (Akhrem et al., 1993; Kisel et al., 1997).

The data obtained in the study of radiolysis of triacetin has shown that completely acetylated derivatives of glycerol did not undergo fragmentation on interaction with radical agents (Akhrem et al., 1993; Kisel et al., 1997):



(9)

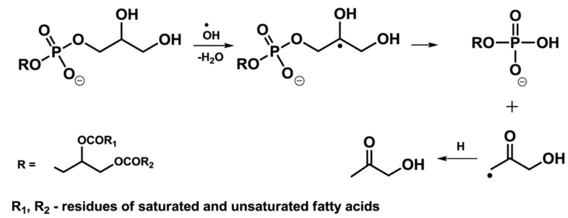
Our subsequent studies of lipids took into account the experimental facts established for glycerides, namely that the tendency to undergo homolytic fragmentation would be observed for those glycerophospholipids, whose structure have hydroxyl groups located in the β-position with respect to the phosphate groups. Lyso-phosphatidylcholine belongs to such phospholipids. Its ability to undergo fragmentation was evaluated by photoselective generation of its C-2 radicals (Müller et al., 1997). In parallel, radiolysis products formed in aqueous solutions of lysolecithin were studied (Edimecheva et al., 1997). The results obtained using both methods indicated the possibility of fragmentation of the lysolecithin radicals. The photoinduced reaction proceeds according to the scheme (10).



(10)

The decomposition rate of C-2 lysolecithin radicals measured using the competitive kinetics method has proven to be $3.8 \times 10^5\ s^{-1}$. This results suggests the possibility of the reaction to take place in biosystems in the presence of oxygen, even at its highest physiological concentrations. Analysis of the final radiolysis products of aqueous dispersions of lysolecithin has shown that phosphocholine was present in greater quantities than palmitoxyacetone (Edimecheva et al., 1997). The phosphocholine was a molecular fragmentation product while the palmitoxyacetone was initially formed as a radical, which must have been consumed in various subsequent reactions.

Further studies of free-radical fragmentation of synthetic and natural glycerophospholipids were carried out using various methods to induce homolytic transformations of the starting compounds with subsequent analysis of the final products by MALDI-TOF-MS technique (Shadyro et al., 2004b; Yurkova et al., 2004a, 2005a, 2006, 2008, 2009). By the example of hydroxyl-containing glycerophospholipids, such as phosphatidyl glycerol (PG) and phosphatidyl inositol (PI), we were shown for the first time that the interaction of OH-radicals with their hydrophilic moiety led to free-radical destruction of C-2 lipid radicals with rupture of β-C—O and O—H bonds (Shadyro, 1997; Shadyro et al., 2004b; Yurkova et al., 2004a, 2005a, 2006). So, phosphatidyl inositol (PI) and phosphatidyl glycerol (PG) containing polyol residues in their hydrophilic moieties undergo free-radical destruction with formation of phosphatidic acid (PA). In the case of (PG), the process occurs as shown below:



(11)

We conclude the fragmentation of the PG radical was produced by simultaneous rupture of two bonds vicinal to the radical center via a cyclic transition state. In studies of free-radical transformations of phosphatidyl choline (PC) and phosphatidyl ethanolamine (PE), which have no OH groups at the α-position to the radical center, PA wasn‘t identified (Edimecheva et al., 1997; Kisel et al., 1997; Yurkova et al., 2004a). This finding indicates that the polar components of these lipids are more resistant to radical agents.

Unlike lipid peroxidation (LPO) processes, which are accelerated with increasing oxygen concentration in the systems, the reactions of free-radical fragmentation (FRF) of hydroxyl-containing compounds are suppressed by oxygen (Shadyro et al., 2002a; Yurkova et al., 2004a, 2006). Therefore, while FRF reactions of glycerophospholipids containing saturated acyl groups were suppressed by oxygen by a factor of 2, this effect was less pronounced for the glycerophospholipids with polyunsaturated acyl groups.

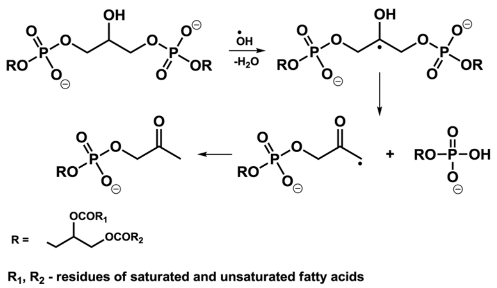
It has been shown (Shadyro et al., 2000) that the yields of lipid fragmentation products decreased about 1.5–2 times in the presence of Ca^{2+} ions. It appears to be an interesting property of these ions, taking into account their important role in the regulation of intracellular processes. Inhibition of FRF reactions by Ca^{2+} ions might be associated with the interaction of positively charged ions with negatively charged phosphate groups, thereby preventing the formation of a cyclic transition state necessary for fragmentation to occur.

Hydroxyl-containing glycerophospholipids containing the residues of unsaturated fatty acids can undergo both fragmentation and oxidation processes (Shadyro et al., 2002a, 2004b; Yurkova et al., 2006). In fact, radiolysis studies of aqueous systems containing such lipids have shown that the radiation-chemical yields of fragmentation products were comparable to those of oxidation products. In deaerated media, the concentration of fragmentation products increased several times as compared to that of LPO products.

On γ-irradiation of PC liposomes it has been shown (Yurkova et al., 2004b) that the presence of PA in the PC liposome composition enhanced the LPO processes occurring in the liposome hydrophobic part. The yield of LPO products for PG, which has a hydroxyl group, was 1.2–1.5 times higher as compared with PC (Yurkova et al., 2004b). Hence, the radiation-induced LPO process is largely accomplished for phospholipids capable of fragmentation in their polar component.

The FRF was found (Shadyro et al., 2004a; Yurkova et al., 2008, 2009) to be a characteristic feature of cardiolipin (CL), polyphospholipids are the main components of mitochondrial membranes. CL is a unique lipid having a dimer structure – it includes four fatty acid residues and two phosphate groups.

During radiolysis, CL was destroyed by breaking the phosphoester bond and forming PA, as well as a radical intermediate, which was reduced to phosphatidyl hydroxyacetone (PHA) and identified by MALDI-TOF-MS (Shadyro et al., 2004a; Yurkova et al., 2008):



(12)

This type of fragmentation was also observed under the action of oxidizing systems containing $Cu^{2+}(Fe^{2+})/H_2O_2$ and $Cu^{2+}(Fe^{2+})/H_2O_2$/ascorbate on CL in both model membranes and mouse liver mitochondria (Shadyro et al., 2004a; Yurkova et al., 2008, 2011). PA formation during radiolysis of PI, PG and CL was most effective for CL, which has two phosphoester groups in β-position to the hydroxyl group. PA is a signaling molecule and plays an important role in the processes of cell proliferation and enhances their resistance to stress (Wang et al., 2006). At the same time, accumulation of PA in cancer cells promotes their survival and proliferation (Foster, 2009). In a living organism, PA is formed in biochemical reactions catalyzed by phospholipase D, diacylglycerol kinase and lysophosphatidic acid acyltransferase (Athenstaedt and Daum, 1999; Bruntz et al., 2014).

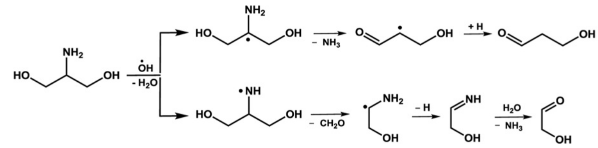
We have discovered a new way to form PA – free-radical fragmentation of CL and other hydroxyl-containing lipids, according to reactions (12) and (13). We believe that the implementation of such reactions in mitochondrial membranes of normal and malignant cells should cause changes in the CL/PA ratio, which affects the functioning of mitochondria and cellular metabolism (Kameoka et al., 2018).

Thus, a characteristic feature of homolytic transformations occurring in hydroxyl-containing glycerophospholipids is the realization of fragmentation processes in carbon-centered radicals, which involve the cleavage of two β-bonds in the polar part of the molecules. This leads to the destruction of such lipids resulting in the formation of bioactive products.

3. Free-radical fragmentation of sphingolipids and related compounds

Free-radical transformations of sphingolipids were of minor interest for specialists working in the areas of biology and medicine. The reason was the absence of fatty acid residues in the structures of lipids of such type, which should make them resistant to oxidation. For this reason, the contribution of sphingolipids to the processes causing damage to biosystems appeared to be negligible. However, sphingolipids have a structural function (Kraft, 2017) and modulate numerous cellular processes, including apoptosis, proliferation and inflammatory signaling pathways (Bartke and Hannun, 2009; Chiantia and London, 2013; Patwardhan et al., 2016). Several studies report that products of sphingolipid metabolism are associated with oxidative stress (de Faria Poloni et al., 2014).

The structure of sphingolipids includes a base fragment - sphingosine, which contains hydroxyl and amino groups. Hence, the polar component of sphingolipids can undergo fragmentation when exposed to ROS. This is concluded by the data obtained in studies of homolytic transformations of serinol and its derivatives, having similar structure to those of the polar component of sphingolipids (Lisovskaya et al., 2009; Lisovskaya et al., 2012; Sladkova et al., 2014). Serinol was shown to undergo deamination and destruction involving the C-N and C-C bond cleavage on interaction with OH radicals, as depicted in the Schemes (13, 14).

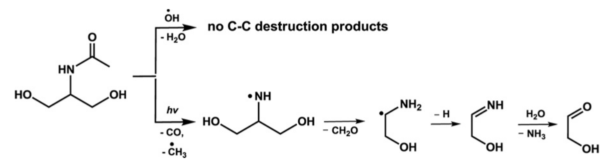


(13)

(14)

The probability ratio for the reactions (13) and (14) was largely dependent on the state of the amine group, which is determined by the pH value of the medium. When the NH_2 group of serinol was not protonated, the destruction process (14) became more probable. Acylation of the amine group in serinol resulted in a drastic decrease in the probability of both of these reactions (Lisovskaya et al., 2012; Sladkova et al., 2014).

However, when irradiated with UV light, N-acylated derivatives of amino alcohols were shown to undergo the Norrish type I degradation, including further C-C bond rupture (15):

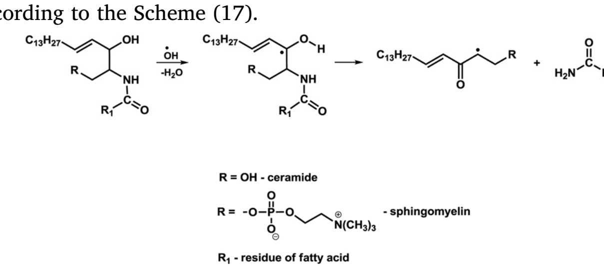


(15)

(16)

Unlike glycerol, the free-radical transformations of serinol proceeded via the formation of both C-centered and N-centered radicals. The presence of the latter was detected by EPR when serinol and its N-acylated derivatives were treated with the Fenton's reagent (Lisovskaya et al., 2018).

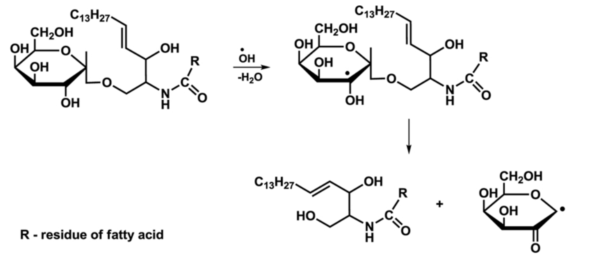
Our first study (Akhrem et al., 1991; Yurkova and Arnhold, 2009) on radiolysis of aqueous dispersions of sphingomyelin and ceramide revealed their ability to decompose and produce fatty acid amides according to the Scheme (17).



(17)

The amide of *cis*-9,10-octadecenoic acid (oleamide) formed in reaction (17) is an endogenous factor inducing sleep in mammals. Besides its action on the central nervous system, oleamide is capable of modulating functions of the immune cells, for example, causing inhibition in lymphocyte proliferation. The inhibiting properties with respect to phospholipase A_2 have been found for the acid amides C(14:3), C(14:2), C(18:3), C(18:2) (Bezuglov et al., 1998).

Studies of homolytic transformations of glycolipids have shown that cerebrosides (galactosyl ceramide, glucosyl ceramide and galactosyl diacylglycerol) underwent destruction under the action of ionizing radiation or the redox systems to form ceramide and diacylglycerid (diacylglycerol) (Shadyro et al., 2004b; Yurkova et al., 2005b). The presence of these products in γ-irradiated aqueous dispersions of the starting glycolipids proves the occurrence of the free-radical fragmentation processes taking place in the lipid molecules, by breaking O-glycoside bonds according to the Scheme (18).

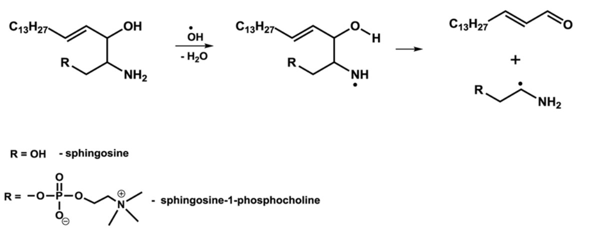


(18)

It was found that similar reactions of glycoside bond cleavage occur during free radical transformations of glycosides, di- and polysaccharides (Shadyro et al., 2007).

The main fragmentation product of galactocerebroside is ceramide. Ceramide is considered to be a critical element of apoptosis, producing marked proapoptotic effects while coming into a direct contact with the cell (Schenck et al., 2007). Ceramide has also been found (Perry and Hannun, 1998) to be a mediator for triggering photoreceptors of apoptosis contained in the eye retina of mammals. It was surmised that modulation of ceramide levels could be used for therapeutical purposes to protect the eye photoreceptors from destruction and neurodegenerative diseases (German et al., 2006).

We have shown in our studies (Lisovskaya et al., 2009, 2011) that γ-irradiation of sphingosine and sphingosine-1-phosphocholine causes their destruction with the C—C bond rupture to give 2-hexadecenal. This aldehyde was not found among radiolysis products of sphingomyelin, hence the presence of a free amine group is an essential requirement for realization of a C—C destruction. Thus, the amine group is apparently directly participating in the destruction process. By comparison with serinol, it may be supposed that this process includes the stage of formation of nitrogen-centered radicals, as presented on by the Scheme (19).



(19)

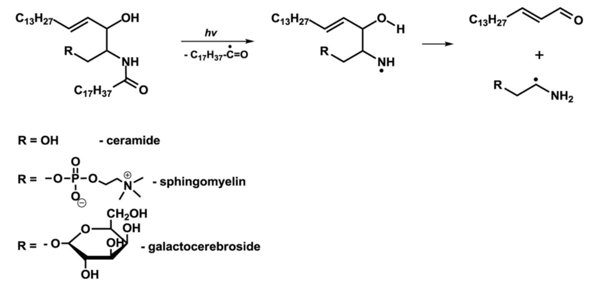
The reaction (19) of sphingolipid destruction is realized due to the formation and subsequent fragmentation of aminyl radicals involving rupture of the C—C bond.

In the case of sphingomyelin, the acyl group reduces the electron density on nitrogen atom due to conjugation with the lone pair, thereby preventing the C—C destruction of this molecule. Therefore, 2-hexadecenal was not formed upon the radiolysis of aqueous dispersions of sphingomyelin.

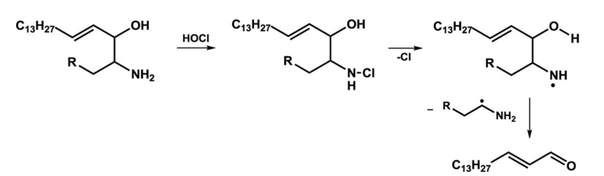
Sphingolipids, like sphingomyelins or ceramides, intrinsically contain photolabile carbonyl group and absorb UV radiation in the 250–300 nm range. Photo-induced transformations of biomolecules are known to result in their modification and/or destruction, and, as a consequence, it may lead to changes in biological functions. There is virtually no information in the literature about photochemical transformations of sphingolipids, although these biomolecules are the main components of the skin epidermis, and hence are directly exposed to UV radiation (Chiantia and London, 2013; Kraft, 2017). Therefore, obtaining such information is of current importance, since it has been established that sphingolipids take part in the transmission of signals during numerous cellular processes (Bartke and Hannun, 2009). Thus, in particular, UV radiation was found to activate sphingomyelinase and to promote transformation of sphingomyelin to ceramide, which participates in the apoptosis processes (Grether-Beck et al., 2008; Magnoni et al., 2002).

Since it has been shown that photolysis of N-acylated aminoalcohols leads to the formation of destruction products, such photo-induced decomposition reactions may be used as an effective method for selective generation of aminyl radicals. These circumstances are additional factors promoting the interest to studying photochemical transformations of sphingolipids and their analogs containing an amide-alcohol moiety in their structures.

Taking into account the data set above, one can suppose that UV irradiation of amide-containing sphingolipids will result in formation of aminyl radicals with their subsequent fragmentation, and accumulation of the C—C-destruction products of the starting lipid according to the Scheme (20).



(20)



(21)

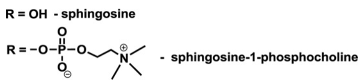
Photolysis of aqueous dispersions of ceramides, sphingomyelins and galactocerebrosides produced products among which 2-hexadecenal was identified. This fact corroborates the staged photodestruction process in sphingolipids as shown above (20).

In the case of sphingosines, containing a free amino group, their photolysis leads to the photodissociation due to n,σ*-transition of N—H bond. It has been found that unsaturated aliphatic aldehydes are the main products formed upon UV irradiation on lysosphingolipids proceeding via C—C bond rupture (Lisovskaya et al., 2017). The photolysis of sphingosine and sphingomyelin with the addition of sensitizers expands the range of photolysis products via the possible formation of N- and C-centered radicals (Lisovskaya et al., 2017).

As shown above, the radiation- and photo-induced destruction of sphingolipids proceeds via the stage of formation of nitrogen-centered radicals. Such intermediates are known to arise from the interaction of hypochlorous acid (HOCl) with amine groups in biomolecules. In particular, formation of nitrogen-centered radicals from aminophospholipids as a result of their interaction with HOCl has been detected using EPR spectrometry (Kawai et al., 2006). Therefore, it was of interest for us to determine the products of destruction of nitrogen-centered radicals of sphingolipids resulting from their interaction with HOCl-generating systems.

Hypochlorous acid (HOCl) is generated in neutrophils during inflammation upon activation of myeloperoxidase (MPO), which triggers the reaction of chloride anion with H_2O_2 as one of the main cellular systems for eradicating microorganisms (Davies, 2011). HOCl being formed in MPO-dependent reactions is characterized by non-specific bactericidal action. Meanwhile, myeloperoxidase may cause damage to tissues during many of inflammatory diseases. So, the MPO levels in blood increase during inflammatory processes in arteria, which may lead to the development of cardiovascular diseases (Nambi, 2005).

For this purpose, we conducted studies of the interactions of lysosphingolipids with both exogeneous HOCl (reagent) and also that generated in the halogenating cycle of MPO, which both have shown that the starting lipids were halogenated to form mono- and dichloro-derivatives. The chloramines formed were unstable and rapidly destroyed leading to accumulation of 2-hexadecenal (Shadyro et al., 2015). Meanwhile among the HOCl and sphingomyelin interactions, only its chlorine derivatives were detected, but 2-hexadecenal was not identified. Based on the total amount of the data resulting from these studies, as well on those obtained in (Kawai et al., 2006), the following scheme has been proposed to propose the process of HOCl-induced formation of 2-hexadecenal from lysosphingolipids (21):



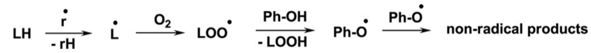
In order to study whether these reactions occur in cultured cells or tissues, which contain sphingolipids under the exposure to radiation or reactive oxygen/chlorinating species, we explored the effects of HOCl in cultured cells. It was found that HOCl induced the formation of 2-hexadecenal in the transplanted cells of rat glioma C6, human embryonic kidney cells and red blood cells (Shadyro et al., 2015). Thus, these studies suggest that the described mechanism of free radical destruction of sphingolipids may be replicated on cell culture under stress of active chlorine forms. It can be assumed that in cases where the level of HOCl increases significantly in the brain during a stroke, traumatic brain injury, tumors, as well as in the cells of the vascular wall and blood cells, the formation of 2-hexadecenal from sphingolipids may occur.

It should be pointed out that there is an enzymatic route for 2-hexadecenal formation. Sphingosine-1-phosphate undergoes irreversible degradation following a biochemical reaction catalyzed by sphingosine-1-phosphate-lyase (SPL), which enhances the process of rupture of the carbon chain of lipid to form 2-hexadecenal and aminoethanol (Serra and Saba, 2010). It was believed earlier that SPL removed S1P away from the sphingolipid metabolic cycle, and the sphingolipid catabolism products - aminoethanol phosphate and 2-hexadecenal – were physiologically inactive. However, later it was shown (Kumar et al., 2011) that 2-hexadecenal is characterized by a wide spectrum of biological activity. It can cause the reorganization of the cellular cytoskeleton, induce apoptosis and form adducts with DNA and provoke mutagenic consequences. Recent studies have revealed, that 2-hexadecenal also regulates redox processes in these cells, and causes a decrease in the proliferative activity of rat glioma C6 cells by reducing fission rate and triggering apoptosis (Amaegberi et al., 2015; Lisovskaya et al., 2014).

These results allowed us to propose a new paradigm of the signal pathways involving sphingolipids, in which the final stage of lipid decomposition to form 2-hexadecenal gave an additional possibility of a 'fine tuning' of the equilibrium between the cell survival and death. The experimental results presented above made it possible to find out new pathways leading to the formation of bioactive 2-hexadecenal from sphingolipids in the course of γ-, UV- and HOCl-induced destruction of the latter. The mechanism includes the stages of formation of nitrogen-centered radicals from sphingolipids and their further destruction via simultaneous rupture of C—C and O—H bonds.

4. Inhibitors of free-radical fragmentation processes in organic molecules

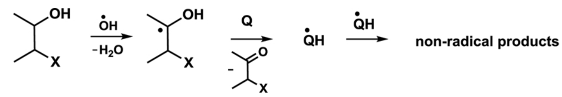
One of the most common methods for inhibition of oxidation processes taking place in various organic substances is using antioxidants. These agents reduce oxygen-centered radicals – the key intermediates in these reactions – generating stable radicals, which would be consumed in possible termination reactions of radical chain processes (Frei, 1994; Halliwell and Gutteridge, 2007). A simplified scheme may be depicted as follows:



(22)

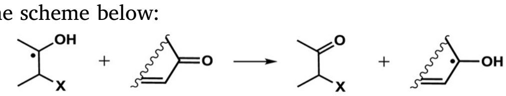
There are numerous natural and synthetic antioxidants, which effectively inhibit oxidation processes, as presented in the scheme (Frei, 1994; Halliwell and Gutteridge, 2007).

Our studies have shown (Samovich et al., 2018; Shadyro et al., 2002b, 2003b, 2005, 2006) that the fragmentation processes occurring in biomolecules can be effectively inhibited by using oxidants such as quinones. The following reactions take place in this case:



(23)

Quinones readily oxidize carbon-centered hydroxyl-containing radicals, thereby blocking their fragmentation processes. So, it has been found that quinones of various structures suppressed formation of PA during free-radical transformations of glycerophospholipids (Shadyro et al., 2002b). Since PA was found (Foster, 2009) to be a promoter for proliferation of cancer cells, this property of substances having structures of quinoid type could be used as a basis for designing antitumor medicines. Subsequent studies (Brinkevich and Shadyro, 2009; Brinkevich et al., 2012, 2013; Hryntsevich and Shadyro, 2005; Lagutin et al., 2005; Samovich et al., 2013; Samovich et al., 2014; Sosnovskaya et al., 2007) revealed that not only quinones, but also other natural substances containing a carbonyl group conjugated with a >C=C< bond, can also inhibit free-radical fragmentation processes, as shown in the scheme below:



(24)

The structural units of this type are present in numerous natural compounds such as flavonoids, curcuminoids, phenylpropanoids, group B vitamins, ascorbic acid, etc.

We have performed studies (Brinkevich and Shadyro, 2009; Brinkevich et al., 2012, 2013; Hryntsevich and Shadyro, 2005; Lagutin et al., 2005; Samovich et al., 2013, 2014; Sosnovskaya et al., 2007) on the effects of natural and synthetic agents having structural units featuring hydroxyl groups and moieties of quinoid type on free-radical transformations of biologically relevant substances and the respective modeling compounds. Substances have been discovered that possess the unique ability to inhibit free-radical processes of both oxidation and fragmentation involving carbon-, nitrogen- and oxygen-centered radicals. Presentation of these results is outside the scope of this review, and it will be the subject of a subsequent paper.

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