ELSEVIER

Biochimica et Biophysica Acta 1411 (1999) 378–384

BIOCHIMICA ET BIOPHYSICA ACTA
BBA

Review

Nitric oxide and lipid peroxidation

Neil Hogg *, B. Kalyanaraman

Biophysics Research Institute, Medical College of Wisconsin, Milwaukee, WI 53226, USA

Received 1 September 1998; received in revised form 20 October 1998; accepted 4 December 1998

Abstract

Nitric oxide can both promote and inhibit lipid peroxidation. By itself, nitric oxide acts as a potent inhibitor of the lipid peroxidation chain reaction by scavenging propagatory lipid peroxyl radicals. In addition, nitric oxide can also inhibit many potential initiators of lipid peroxidation, such as peroxidase enzymes. However, in the presence of superoxide, nitric oxide forms peroxynitrite, a powerful oxidant capable of initiating lipid peroxidation and oxidizing lipid soluble antioxidants. The role of nitric oxide in vascular pathology is discussed.

Contents

1. Introduction

Oxidative stress can be considered to occur when the flux of partially reduced forms of oxygen is great-

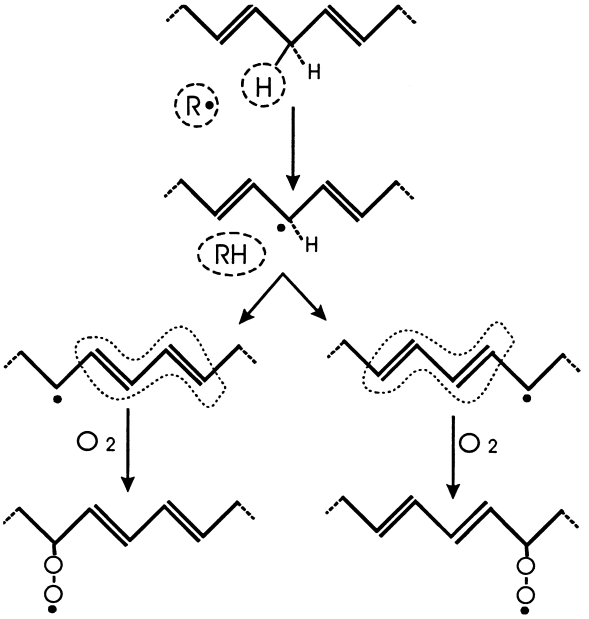
* Corresponding author.

0005-2728/99/$ – see front matter
PII: S0005-2728(99)00027-4

er than the ability of the biological system to cope with their production. Under stressed conditions, biological molecules are exposed to pro-oxidant species resulting in irreversible oxidation reactions. Such reactions result in chemical modification of biological molecules that can lead to cellular dysfunction. Oxidative damage to nuclear DNA can result in gene mutation and is thought to be one cause of carcinogenesis [1,2]. Protein oxidative damage is generally less of a concern as most proteins turn over rapidly. However, in situations such as the lens, where the crystallins have a slow turnover rate, oxidative damage will be cumulative and is thought to lead to cataract development [3]. In addition, the 'redox status' of a cell, which refers to the ratio of the reduced and oxidized forms of certain cellular components (e.g., glutathione), is an important signaling device in cellular homeostasis [4]. It follows that any additional oxidative insult that changes the redox-status of the cell will consequently alter the expression and activity of cellular metabolic pathways.

Lipid bilayer membranes define the extent of cells and organelles. The permeability characteristics of the bilayer allow gradients of metabolite and electrolyte concentrations to exist between the intra- and extracellular spaces. Any loss in membrane integrity due to lipid damage will rapidly dissipate these gradients and compromise cellular function. For example, the loss and the inner mitochondrial membrane permeability barrier would preclude the establishment of a proton gradient and prevent ATP synthesis. Lipids are also subject to turnover under normal conditions, and damaged lipids can be reprocessed and repaired. However, many of the products of lipid oxidation, such as hydroperoxides, alcohols, aldehydes and F2-isoprostanes, have biological activities beyond concerns about barrier function [5,6]. In addition, lipid oxidation is a chain reaction. A single oxidative event can oxidize many lipid molecules. In the presence of iron or copper ions, the chain reaction can become a cascade and the oxidation process can rapidly become unstoppable [7]. Biological strategies against lipid peroxidation involve both preventing the initial oxidation and breaking the chain before much damage is done.

This review will focus on the role of nitric oxide in promoting and inhibiting lipid oxidation reactions.



Scheme 1. Lipid peroxidation. Abstraction of an allylic hydrogen and conjugated diene formation.

2. Mechanism of lipid oxidation

Polyunsaturated fatty acids have a propensity to oxidize, resulting in the formation of alkanes, aldehydes, alcohols, and hydroperoxides among other products. This propensity arises from the fact that bis-allylic methylene hydrogens are more susceptible to hydrogen abstraction by oxidizing radicals than are the methylene hydrogens from fully saturated lipids. This is partially due to the fact that the resulting free radical has multiple resonance structures that increase its stability (Scheme 1). In the more heavily populated of these structures the double bonds are conjugated and the radical resides on an adjacent methylene carbon. The rapid reaction of these resonance forms with oxygen 'fixes' the double bonds in a conjugated arrangement to form peroxyl radicals at positions +2 and −2 with respect to the carbon atom from which the original abstraction occurred (Scheme 1). For example, oxidation of linolenic acid by hydrogen abstraction at carbon-11 can result in peroxyl radicals at both the 9- and 13-position. The conjugation of the double bond results in a red-shift of the UV absorbance spectrum to give a maximum at 234 nm. This change is often employed in vitro and in vivo to detect and quantify lipid oxidation.

The lipid peroxyl radical is the central species of the lipid peroxidation chain reaction. This radical can abstract a bis-allylic hydrogen from an adjacent fatty acid to form a lipid hydroperoxide and a second lipid radical (Eq. 1), which subsequently reacts with oxygen to regenerate a peroxyl radical (Eq. 2).

$$LOO\bullet + LH \rightarrow LOOH + L\bullet \quad (1)$$

$$L\bullet + O_2 \rightarrow LOO\bullet \quad (2)$$

These reactions are the chain-propagation steps of lipid peroxidation. Eq. 1 is rate limiting and so the rate of the propagation reaction is proportional to the concentration of lipid peroxyl radicals. Consequently any reaction that alters the concentration of peroxyl radicals will affect the rate of lipid peroxidation.

3. Factors affecting lipid peroxyl radical concentration

Lipid peroxyl radical concentration can be altered by a number of factors.

3.1. Transition metal ions

A few ions of transition metal elements have redox transitions with potentials of a magnitude that allows the catalytic decomposition of hydroperoxides. The redox couples of most importance to biological systems are Cu^{+}/Cu^{2+} and Fe^{2+}/Fe^{3+}. The one electron redox cycle results in the formation of peroxyl and alkoxyl radicals [8], the latter of which rearrange and react with oxygen to form peroxyl radicals [9]. By this mechanism, transition metal ions increase the concentration of peroxyl radicals and accelerate lipid peroxidation. As lipid peroxidation generates lipid hydroperoxides, the effect of transition metal ions is autocatalytic. This behavior is observed during copper catalyzed oxidation of low-density lipoprotein [10,11].

3.2. Termination reactions

In the absence of any additional reactions, the lipid peroxidation chain reaction will terminate when two lipid radicals react to form non-radical products. These reactions decrease the level of peroxyl radicals and slow the rate of lipid oxidation. The mechanism and products of such reactions are complex and only partially understood. It has been reported that endogenous chemiluminescence is associated with such reactions, perhaps indicating the formation of singlet state oxygen [12].

3.3. Antioxidants

As demonstrated in Eq. 1, lipid peroxyl radicals propagate the chain reaction of lipid peroxidation by abstracting a hydrogen atom from an unsaturated fatty acid. It follows that any compound that can donate a hydrogen atom to the peroxyl radical should be able to break, or at least divert, the chain of reaction. Compounds that donate a hydrogen to leave a relatively inert radical product are referred to as chain-breaking antioxidants. The most well known and well-studied chain-breaking antioxidants are phenolic compounds, such as the natural tocopherols [13].

4. The role of nitric oxide in lipid oxidation

As discussed above, the rate of lipid peroxidation depends strongly on the concentration of peroxyl radicals. Consequently, any discussion of the role of nitric oxide in lipid peroxidation can be simplified by asking the question 'how does nitric oxide affect lipid peroxyl radical concentration?' This question can be addressed at several levels.

4.1. Nitric oxide and the initiation of lipid peroxidation

The mechanisms by which the initiation of lipid peroxidation occurs in vivo are not well defined but are likely to be a subset of the mechanisms that have been carefully studied in vitro [10,14,15]. In addition, some clearly non-physiological models for the initiation of lipid peroxidation have given invaluable insights into this process [16]. Nitric oxide is not a strong oxidant and cannot extract a bis allylic hydrogen from an unsaturated fatty acid to begin the peroxidation chain reaction [14]. However, in combination with other agents nitric oxide can both promote and inhibit the initiation of lipid oxidation. The role

of nitric oxide in the initiation of lipid peroxidation can be subdivided as follows.

4.1.1. Nitric oxide and pro-oxidant enzymes and proteins

Several enzymes have the ability to oxidize unsaturated fatty acids. The complex pathways of arachidonate metabolism to form prostaglandins, leukotrienes and related species contain enzymes that catalyze the introduction of dioxygen, either as an endoperoxide (in the case of cyclooxygenase) or as a hydroperoxide (in the case of lipoxygenases). In addition, several cytochrome *P*450 type enzymes are also involved in arachidonate oxidation. Nitric oxide has been suggested to inhibit these enzymes by reduction of active site heme or non-heme iron to an inactive ferrous form [17]. These observations suggest interplay between the nitric oxide pathway and arachidonate metabolism.

Lipid oxidation can also be initiated by ferryl hemoglobin, formed from the interaction of hemoglobin with peroxides. Nitric oxide has been shown to reduce the ferryl heme and so prevent lipid oxidation by this mechanism [18,19].

4.1.2. Nitric oxide and glutathione peroxidase

Glutathione peroxidases are glutathione-dependent seleno peroxidases that catalyze the reduction of hydroperoxides to the respective alcohols. It has been reported that glutathione peroxidase can be inhibited by the putative nitric oxide donor *S*-nitroso-*N*-acetyl penicillamine (SNAP) in U937 cells and that this inhibition leads to an increased level of lipid peroxidation [20]. The mechanism for this effect was determined to be oxidation of the selenocysteine of the peroxidase to a selenocystine–cystine bridge [21]. Nitric oxide may thus interfere with the detoxification of hydroperoxides once formed.

4.1.3. Nitric oxide and chemical initiators

The hydroxyl radical (•OH) is a highly oxidizing free radical and will initiate lipid peroxidation by hydrogen abstraction. Hydroxyl radicals are thought to be generated in vivo from the combination of iron ions (or copper ions), hydrogen peroxide and a reducing agent (e.g., ascorbate) by the Fenton reaction. This mixture is an aggressive oxidant and will oxidize many biological molecules, including unsaturated fatty acids. The high reactivity of the hydroxyl radical makes it a relatively unselective oxidant and reacts with many biomolecules at rates approaching the diffusion limit. This means that in order for any scavenger to have a competitive advantage as a hydroxyl radical scavenger it has to be present in millimolar concentrations. Nitric oxide will react with the hydroxyl radical at diffusion limited rates to generate nitrite, but it clearly cannot exist in vivo at a high enough concentration to be an effective scavenger. Nitric oxide has been shown to inhibit the Fenton reaction by binding to ferrous iron and thus preventing the formation of hydroxyl radical [22]. The relevance of this mechanism to in vivo conditions has not been established.

4.1.4. Peroxynitrite

In addition to inhibiting the initiation of lipid peroxidation, nitric oxide may also enhance this process. The reaction between nitric oxide and superoxide generates peroxynitrite [23]. This molecule is a powerful oxidant that exhibits complex chemistry with biological molecules. Reaction of peroxynitrite with unsaturated fatty acid-containing liposomes results in the initiation of lipid peroxidation [14,24]. In addition, exposure of low-density lipoprotein to either peroxynitrite [25] or SIN-1 [14] (a compound that generates nitric oxide and superoxide simultaneously [26]) results in the oxidation of unsaturated fatty acids. The mechanism of initiation is unclear but may involve either abstraction of a bis-allylic hydrogen by the 'the hydroxyl radical-like' activity peroxynitrite, or induced homolysis of peroxynitrite by the unsaturated fatty acid.

Peroxynitrite will also rapidly oxidize tocopherols. Consequently, in a lipid membrane, one of the first actions of peroxynitrite is to remove the endogenous low molecular mass antioxidant protection mechanism. α-Tocopherol is oxidized by two electrons to α-tocopheryl quinone, a form that is not easily repaired by cellular reductants [27].

4.1.5. Nitrogen dioxide

The reaction between nitric oxide and molecular oxygen generates nitrogen dioxide (•NO_2), in combination with radical–radical combination products, dinitrogen trioxide and dinitrogen tetroxide. It has been known for some time the nitrogen dioxide is

able to initiate lipid peroxidation [28]. The question of whether the reaction of nitric oxide with oxygen is biologically relevant is an ongoing debate.

4.2. Nitric oxide and the propagation of lipid peroxidation

As mentioned above, the rate of propagation of lipid peroxidation depends strongly on the steady state concentration of lipid peroxyl radicals. It has been demonstrated that the radical–radical reaction between nitric oxide and organic peroxyl radicals is almost diffusion limited and generates a transient ROONO species. This species is thought to undergo homolytic cleavage to give an alkoxyl radical (RO•) and nitrogen dioxide [29]. The rate constant for this reaction in aqueous solution has been determined to be $1–3\times10^9$ [30]. It may be thought, therefore, that nitric oxide would enhance lipid peroxidation as both the alkoxyl radical and nitrogen dioxide are able to oxidize unsaturated lipid. However, experiment has demonstrated that nitric oxide is a potent inhibitor of the propagation reaction [31] [32–36]. The most likely explanation for this observation is peroxyl radical scavenging. It was recently demonstrated that the stoichiometry of the reaction between nitric oxide and peroxyl radical is approximately 2:1 [37]. It was suggested that ROONO has two fates; (i) internal rearrangement to give the more stable $RONO_2$ (a 1:1 stoichiometry) and (ii) homolytic cleavage of the O–O bond to give RO• and nitrogen dioxide. Either the alkoxyl radical, or a product of this radical (such as an epoxyallylic–peroxyl radical) would be expected to propagate lipid peroxidation. However these species may further react with nitric oxide to prevent propagation. Nitrogen dioxide is also known to react with nitric oxide to generate dinitrogen trioxide which, in the absence of any other target, will hydrolyze to nitrite anion. This second pathway has a stoichiometry of 3:1 or 4:1. A combination of the above pathways was suggested to be responsible for the observed 2:1 stoichiometry [37].

5. Nitric oxide and lipid oxidation in pathophysiology

In light of the potent inhibitory effect of nitric oxide on the propagation of lipid peroxidation, it is not certain that the lipid peroxidation chain reaction could ever proceed in the presence of physiological concentrations of nitric oxide. Kinetic considerations imply that nitric oxide is a $10^4–10^5$ times more potent peroxyl radical scavenger than is α-tocopherol, and it has been demonstrated that the slow generation of nitric oxide is able to inhibit the oxidation of α-tocopherol upon exposure to oxidants [36].

Although lipid peroxidation has been implicated to be a deleterious component of many oxidative inflammatory disorders, in most cases lipid oxidation has not been regarded as a causative step in the progression of the disease. One exception to this is atherogenesis, where lipid oxidation has been suggested to be a mechanistic component of the formation of fatty streaks and atheroma [38]. It follows, therefore, that nitric oxide should play a protective role in atherosclerosis. All available evidence to date suggests that compromised endothelial nitric oxide formation is an early lesion in atherosclerosis and that the disease can be ameliorated by restoration of nitric oxide synthesis [39–41]. In addition, chronic inhibition of nitric oxide formation is pro-atherogenic in cholesterol fed rabbits [42,43]. Although nitric oxide may work at several levels during atherosclerosis, it is possible that its initial protective effect is the suppression of lipid oxidation. It has been demonstrated that nitric oxide is a potent inhibitor of LDL oxidation when initiated by both cellular and chemical systems [31,44,45]. In addition, nitric oxide can protect cells against the toxic effects of oxidized LDL on endothelial cells [46].

Elevation of endothelial superoxide generation, by several mechanisms, is thought to be an initial component of the atherosclerotic process [47]. In addition, a substantial body of evidence suggests that nitric oxide and superoxide react rapidly in biological systems. It follows that superoxide elevation will result in a decrease in nitric oxide levels. Reduction in available nitric oxide will reduce any beneficial effects in the suppression of lipid peroxidation. In addition, the peroxynitrite that is formed from the reaction between nitric oxide and superoxide may add to the oxidative stress in the vessel wall. Elevation of endothelial superoxide is consequently a double-edged sword [48].

6. Conclusions

The multiple effects of nitric oxide on the process of lipid peroxidation imply that the net result will depend on the balance of competing factors. The rate and location of nitric oxide formation, and also the rate of formation of superoxide, or other mitigating factors, will all contribute to the degree of lipid oxidation in a particular system. It is highly likely, however, that the basal activity of endothelial nitric oxide synthase represents an antioxidant mechanism to suppress lipid peroxidation and any consequent cardiovascular dysfunction.

Acknowledgements

We would like to thank Drs Ravinder J. Singh, Eugene A. Konorev and Steven P. Goss for many useful discussions. This work was supported by National Institutes of Health grants GM55792, GM22923, from the National Institute of General Medicine, and HL47250 from the National Heart-Lung Institute.

References

[1] J.F. Ward, The complexity of DNA damage: relevance to biological consequences, Int. J. Radiat. Biol. 66 (1994) 427–432.
[2] P. Hochstein, A.S. Atallah, The nature of oxidants and antioxidant systems in the inhibition of mutation and cancer, Mutat. Res. 202 (1988) 363–375.
[3] A. Taylor, K.J. Davies, Protein oxidation and loss of protease activity may lead to cataract formation in the aged lens, Free Radic. Biol. Med. 3 (1987) 371–377.
[4] H. Nakamura, K. Nakamura, J. Yodoi, Redox regulation of cellular activation, Annu. Rev. Immunol. 15 (1997) 351–369.
[5] H. Esterbauer, R.J. Schaur, H. Zollner, Chemistry and biochemistry of 4-hydroxynonenal, malonaldehyde and related aldehydes, Free Radic. Biol. Med. 11 (1991) 81–128.
[6] K.P. Moore, V. Darley-Usmar, J. Morrow, L.J. Roberts, Formation of F2-isoprostanes during oxidation of human low-density lipoprotein and plasma by peroxynitrite, Circ. Res. 77 (1995) 335–341.
[7] B. Halliwell, J.M. Gutteridge, Oxygen toxicity, oxygen radicals, transition metals and disease, Biochem. J. 219 (1984) 1–14.
[8] A.W. Girotti, Mechanism of lipid peroxidation, Free Radic. Biol. Med. 1 (1985) 87–95.
[9] A.L. Wilcox, L.J. Marnett, Polyunsaturated fatty acid alkoxyl radicals exist as carbon-centered epoxyallylic radicals: a key step in hydroperoxide-amplified lipid peroxidation, Chem. Res. Toxicol. 6 (1993) 413–416.
[10] H. Esterbauer, J. Gebicki, H. Puhl, G. Jurgens, The role of lipid peroxidation and antioxidants in oxidative modification of LDL, Free Radic. Biol. Med. 13 (1992) 341–390.
[11] V. O'Leary, A. Graham, V. Darley-Usmar, D. Stone, The effect of lipid hydroperoxides on the copper dependent oxidation of low density lipoprotein, Biochem. Soc. Trans. 21 (1993) 89S.
[12] K. Sugioka, M. Nakano, A possible mechanism of the generation of singlet molecular oxygen in NADPH-dependent microsomal lipid peroxidation, Biochim. Biophys. Acta 423 (1976) 203–216.
[13] D.C. Liebler, The role of metabolism in the antioxidant function of vitamin E, Crit. Rev. Toxicol. 23 (1993) 147–169.
[14] V.M. Darley-Usmar, N. Hogg, V.J. O'Leary, M.T. Wilson, S. Moncada, The simultaneous generation of superoxide and nitric oxide can initiate lipid peroxidation in human low density lipoprotein, Free Radic. Res. Commun. 17 (1992) 9–20.
[15] E. Wieland, S. Parthasarathy, D. Steinberg, Peroxidase-dependent metal-independent oxidation of low density lipoprotein in vitro: a model for in vivo oxidation?, Proc. Natl. Acad. Sci. USA 90 (1993) 5929–5933.
[16] N. Noguchi, N. Gotoh, E. Niki, Dynamics of the oxidation of low density lipoprotein induced by free radicals, Biochim. Biophys. Acta 1168 (1993) 348–357.
[17] J. Kanner, S. Harel, R. Granit, Nitric oxide, an inhibitor of lipid oxidation by lipoxygenase, cyclooxygenase and hemoglobin, Lipids 27 (1992) 46–49.
[18] G. Dee, C. Rice-Evans, S. Obeyesekera, S. Meraji, M. Jacobs, K.R. Bruckdorfer, The modulation of ferryl myoglobin formation and its oxidative effects on low density lipoproteins by nitric oxide, FEBS Lett. 294 (1991) 38–42.
[19] N.V. Gorbunov, A.N. Osipov, B.W. Day, B. Zayas-Rivera, V.E. Kagan, N.M. Elsayed, Reduction of ferrylmyoglobin and ferrylhemoglobin by nitric oxide: a protective mechanism against ferryl hemoprotein-induced oxidations, Biochemistry 34 (1995) 6689–6699.
[20] M. Asahi, J. Fujii, K. Suzuki, H.G. Seo, T. Kuzuya, M. Hori, M. Tada, S. Fujii, N. Taniguchi, Inactivation of glutathione peroxidase by nitric oxide. Implication for cytotoxicity, J. Biol. Chem. 270 (1995) 21035–21039.
[21] M. Asahi, J. Fujii, T. Takao, T. Kuzuya, M. Hori, Y. Shimonishi, N. Taniguchi, The oxidation of selenocysteine is involved in the inactivation of glutathione peroxidase by nitric oxide donor, J. Biol. Chem. 272 (1997) 19152–19157.
[22] J. Kanner, S. Harel, R. Granit, Nitric oxide as an antioxidant, Arch. Biochem. Biophys. 289 (1991) 130–136.
[23] J.S. Beckman, T.W. Beckman, J. Chen, P.A. Marshall, B.A. Freeman, Apparent hydroxyl radical production by peroxynitrite: implications for endothelial injury from nitric oxide and superoxide, Proc. Natl. Acad. Sci. USA 87 (1990) 1620–1624.

[24] R. Radi, J.S. Beckman, K.M. Bush, B.A. Freeman, Peroxynitrite-induced membrane lipid peroxidation: the cytotoxic potential of superoxide and nitric oxide, Arch. Biochem. Biophys. 288 (1991) 481–487.
[25] A. Graham, N. Hogg, B. Kalyanaraman, V. O'Leary, V. Darley-Usmar, S. Moncada, Peroxynitrite modification of low-density lipoprotein leads to recognition by the macrophage scavenger receptor, FEBS Lett. 330 (1993) 181–185.
[26] N. Hogg, V.M. Darley-Usmar, M.T. Wilson, S. Moncada, Production of hydroxyl radicals from the simultaneous generation of superoxide and nitric oxide, Biochem. J. 281 (1992) 419–424.
[27] N. Hogg, V.M. Darley-Usmar, M.T. Wilson, S. Moncada, The oxidation of alpha-tocopherol in human low-density lipoprotein by the simultaneous generation of superoxide and nitric oxide, FEBS Lett. 326 (1993) 199–203.
[28] D.F. Church, W.A. Pryor, Free-radical chemistry of cigarette smoke and its toxicological implications, Environ. Health Perspect. 64 (1985) 111–126.
[29] R. Atkinson, S.M. Aschmann, J.N. Pitts Jr., Alkyl nitrate formation from the NO_x-air photooxidations of C_2–C_8 n-alkanes, J. Phys. Chem. 86 (1982) 4563–4587.
[30] S. Padmaja, R.E. Huie, The reaction of nitric oxide with organic peroxyl radicals, Biochem. Biophys. Res. Commun. 195 (1993) 539–544.
[31] N. Hogg, B. Kalyanaraman, J. Joseph, A. Struck, S. Parthasarathy, Inhibition of low-density lipoprotein oxidation by nitric oxide. Potential role in atherogenesis, FEBS Lett. 334 (1993) 170–174.
[32] H. Rubbo, R. Radi, M. Trujillo, R. Telleri, B. Kalyanaraman, S. Barnes, M. Kirk, B.A. Freeman, Nitric oxide regulation of superoxide and peroxynitrite-dependent lipid peroxidation. Formation of novel nitrogen-containing oxidized lipid derivatives, J. Biol. Chem. 269 (1994) 26066–26075.
[33] H. Rubbo, S. Parthasarathy, S. Barnes, M. Kirk, B. Kalyanaraman, B.A. Freeman, Nitric oxide inhibition of lipoxygenase-dependent liposome and low-density lipoprotein oxidation: termination of radical chain propagation reactions and formation of nitrogen-containing oxidized lipid derivatives, Arch. Biochem. Biophys. 324 (1995) 15–25.
[34] K. Hayashi, N. Noguchi, E. Niki, Action of nitric oxide as an antioxidant against oxidation of soybean phosphatidylcholine liposomal membranes, FEBS Lett. 370 (1995) 37–40.
[35] S.P. Goss, N. Hogg, B. Kalyanaraman, The antioxidant effect of spermine NONOate in human low-density lipoprotein, Chem. Res. Toxicol. 8 (1995) 800–806.
[36] S.P. Goss, N. Hogg, B. Kalyanaraman, The effect of nitric oxide release rates on the oxidation of human low density lipoprotein, J. Biol. Chem. 272 (1997) 21647–21653.
[37] V.B. O'Donnell, P.H. Chumley, N. Hogg, A. Bloodsworth, V.M. Darley-Usmar, B.A. Freeman, Nitric oxide inhibition of lipid peroxidation: kinetics of reaction with lipid peroxyl radicals and comparison with alpha-tocopherol, Biochemistry 36 (1997) 15216–15223.
[38] D. Steinberg, S. Parthasarathy, T.E. Carew, J.C. Khoo, J.L. Witztum, Beyond cholesterol. Modifications of low-density lipoprotein that increase its atherogenicity, N. Engl. J. Med. 320 (1989) 915–924.
[39] A.J. Maxwell, J.P. Cooke, Cardiovascular effects of L-arginine, Curr. Opin. Nephrol. Hypertens. 7 (1998) 63–70.
[40] J.P. Cooke, J. Dzau, A. Creager, Endothelial dysfunction in hypercholesterolemia is corrected by L-arginine, Basic Res. Cardiol. 86, (Suppl 2) (1991) 173–181.
[41] R.C. Candipan, B.Y. Wang, R. Buitrago, P.S. Tsao, J.P. Cooke, Regression or progression. Dependency on vascular nitric oxide, Arterioscler. Thromb. Vasc. Biol. 16 (1996) 44–50.
[42] A.J. Cayatte, J.J. Palacino, K. Horten, R.A. Cohen, Chronic inhibition of nitric oxide production accelerates neointima formation and impairs endothelial function in hypercholesterolemic rabbits, Arteroiscler. Thromb. 14 (1994) 753–759.
[43] K. Naruse, K. Shimizu, M. Muramatsu, Y. Toki, Y. Miyazaki, K. Okumura, H. Hashimoto, T. Ito, Long-term inhibition of NO synthesis promotes atherosclerosis in the hypercholesterolemic rabbit thoracic aorta. PGH_2 does not contribute to impaired endothelium-dependent relaxation, Arteroiscler. Thromb. 14 (1994) 746–752. [see comments]
[44] N. Hogg, A. Struck, S.P. Goss, N. Santanam, J. Joseph, S. Parthasarathy, B. Kalyanaraman, Inhibition of macrophage-dependent low density lipoprotein oxidation by nitric-oxide donors, J. Lipid Res. 36 (1995) 1756–1762.
[45] U. Malo-Ranta, S. Yla-Herttuala, T. Metsa-Ketela, O. Jaakkola, E. Moilanen, P. Vuorinen, T. Nikkari, Nitric oxide donor GEA 3162 inhibits endothelial cell-mediated oxidation of low density lipoprotein, FEBS Lett. 337 (1994) 179–183.
[46] A.T. Struck, N. Hogg, J.P. Thomas, B. Kalyanaraman, Nitric oxide donor compounds inhibit the toxicity of oxidized low-density lipoprotein to endothelial cells, FEBS Lett. 361 (1995) 291–294.
[47] Y. Ohara, T.E. Peterson, D.G. Harrison, Hypercholesterolemia increases endothelial superoxide anion production, J. Clin. Invest. 91 (1993) 2546–2551.
[48] V. Darley-Usmar, B. Halliwell, Blood radicals: reactive nitrogen species, reactive oxygen species, transition metal ions, and the vascular system, Pharm. Res. 13 (1996) 649–662.