Chapter 14

Tissue Occurrence of Carbonyl Products of Lipid Peroxidation and Their Role in Inflammatory Disease

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Additional information is available at the end of the chapter

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1. Introduction

The lipid peroxidation is a diffuse process which regards the polyunsaturated fatty acids of lipids, when they are exposed to oxygen-derived free radicals.

The process occurs when oils or foods, vegetables or meats, or other materials are exposed to air and causes their alteration at least in part through the peroxidative decomposition of the fatty acids contained in their lipids.

The lipid peroxidation does not need the action of enzymes and brings to the progressive decomposition of the unsaturated fatty acids till to the formation of carbonylic end products, aldehydes and ketones.

Oxygen-derived free radicals can be produced by the effect of sun rays on O_2, but an important source of them is the cellular metabolism, too.

The interest and the importance of the lipid peroxidation arise from the fact that the polyunsaturated fatty acids are contained in the phospholipids present in all cellular membranes; their structure and function can be strongly modified by this process.

The cellular effects of the lipid peroxidation change according to its degree. A high lipoperoxidative rate can produce serious damages to the cells and their death; on the contrary, a low degree of it allows cell survival and may modulate tissue metabolism.

2. Steps of the lipoperoxidative process

The lipid peroxidation has many steps,as shown in the Figure 1. The process is started by the attach of free radicals to poly-unsaturated fatty acids of lipids. Free radicals are chemical

species which have a single, unpaired electron in an outer orbit. Their molecular configuration is unstable and so they react with the adjacent molecules to acquire a more stable configuration. The polyunsaturated fatty acids contained in the phospholipids of cell membranes are a good target for their reaction; in the attach of free radicals to the unsaturated fatty acids of lipids a methylen group near a double bond can give the electron required by the free radical to form the electon pair. So the unsaturated fatty acid has become a free radical and reacts with another molecule, starting the propagation phase which characterizes the lipoperoxidative process. In our cells the molecular oxygen is always present and can react with the lipid radical to form a lipoperoxide. This molecule has un unstable configuration too. The formed lipoperoxides react with adjacent membrane molecules, either other lipids or proteins. The reaction of a lipoperoxide with a protein molecule changes it in a reactive free radical; the so activated protein can interact with another protein to give a protein complex or interacts with lipids to form lipofuscin molecules. The presence of lipofuscin is frequent in the tissues of old people; this fact was well known by the anatomists already in the past century; the mechanism of their formation has been clarified with the discovery of the lipoperoxidative process. Beside the reaction with other molecules, the lipoperoxides can break to give more stable end products, aldehydes and ketones. These carbonylic end products of lipid peroxidation are formed above all in the microsomes where the rate of the lipid peroxidation is strong, but they can diffuse and react with various molecular targets both within the cell and outside it.

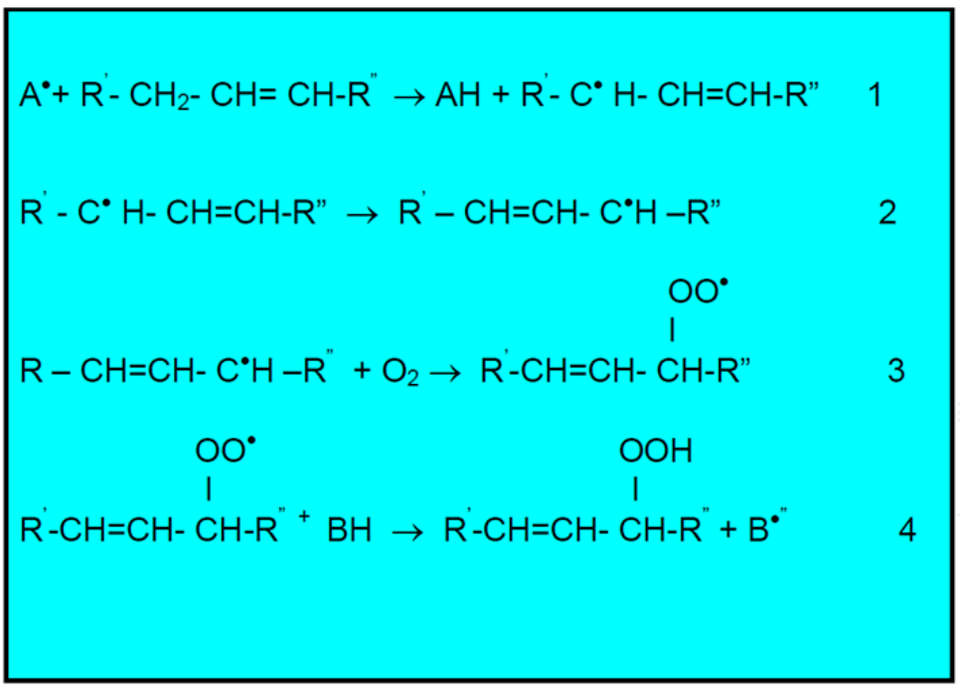

Figure 1. First steps of the lipid peroxidative process. 1) The free radical A• abstracts an electron from a near molecule, which becomes a free radical; the target molecule is often a polyunsaturated fatty acid. 2) Its molecular configuration is unstable, so a shift of the double bond occurs. 3) This still unstable free radical binds O_2 and becomes a peroxide. 4) The peroxide captures an electron from the molecule B and forms an hydro-peroxide. Now the molecule B is a free radical. The further fate of the hydroperoxide is its fragmentation in small carbonylic compounds (not shown iin the Figure)

The first reports of the actual occurrence of the lipid peroxidation in tissues include the researches separately carried on by Comporti M et al.[1] and by Recknagel RO and Ghoshal AK. [2] to explain the liver damage induced by the rat treatment with CCl_4. Both these works used methods of investigation quite modern for those years and brought important findings to understand the structure and the functions of the different cell compartments: nucleus, mithochondria, microsomes, lysosomes. The further experimental studies on the steps and the effects of the lipid peroxidation have been deeply facilitated by Benedetti al. [3] who were able to develop a method to synthetize its carbonylic end-products, above all the aldehyde 4-hydroxy-2,3-trans-nonenal (HNE), whose chemical structure is shown in the Figure 2. HNE was shown to be produced in good amounts when the lipid peroxidation was stimulated; furthermore several experimental researches found that this aldehyde was the more cytotoxic end product of the lipoperoxidative process [4]. The first experimental works on the effects used millimolar concentrations of the aldehyde which were rather high; later the researchers found that it could display several biological effects at concentrations micromolar or less, which can be easily found in tissues even in normal conditions.

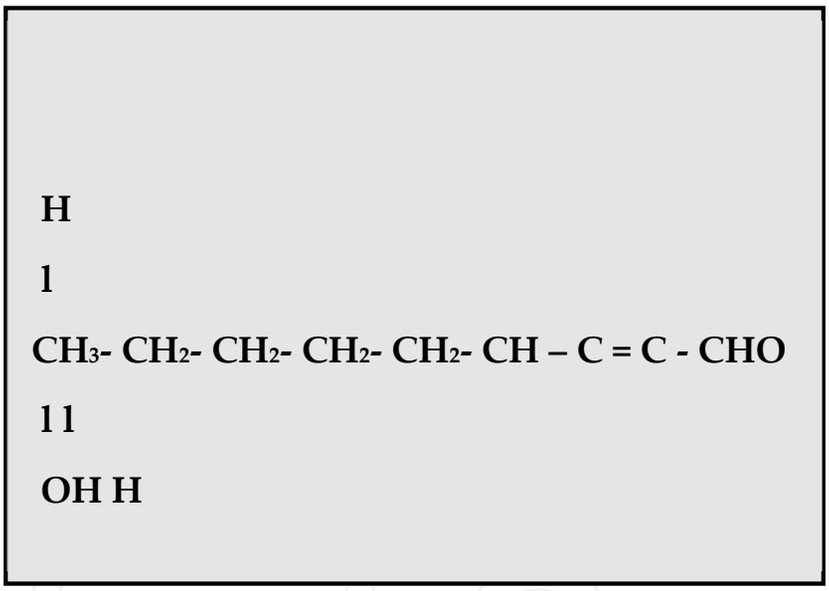

Figure 2. Structure of 4-hydroxy-2,3-trans-nonenal.

3. Lipoperoxidative effects on cell compartments

The damage to the different cell structures induced by the rat treatment with CCl_4 are similar to the alterations found in different pathological processes and are followed by similar changes in the tissue metabolism. In fact all the cell structures, mithocondria, microsomes, lysosomes, nuclei, are delimitated by membranes where the lipid peroxidation can take place and cause damage, bringing to changes in their functions. a) Effects of the lipid peroxidation on microsomes. The action of toxic compounds on cells leads to a quite rapid swelling of rough and smooth endoplasmic reticulum; the ribosomes dissociate from the rough endoplasmic reticulum and the protein synthesis decreases within less than 30 minutes [5,6]. The inhibition of microsomal glucose-6-phosphatase activity is seen very early

in the action of toxic compounds; afterwords the activity of several other enzymes (hexokinase, lactate dehydrogenase, alpha and beta polymerases, 5'nucleotidase) has been found to decrease under the effect of the end products of the lipid peroxidation. However the effects of the inhibition of the protein synthesis can be seen only after different hours because the cells have a reserve of preformed proteins which can be used. The microsomes are the site of the drug metabolizing enzyme system (d.m.e.s.) which metabolizes different compounds, either endogenous components, such as different hormones, or various xenobiotics. The result of the changes induced by the d.m.e.s. on a compound can be different: the compound can be inactivated, it can change its functions or it can even acquire a toxic action. . . . CCl_4 has solvent properties in high amounts, but much smaller quantities can induce biological toxic effects through its homolitical cleavage catalysed by the d.m.e.s. In fact CCl_4 fission generates free radicals able to trigger the lipid peroxidative process, starting from microsomal membranes. In the rats intoxicated with CCl_4 an early effect is the decrease of the hepatic content of cytochrome P_{450}, which is part of the d.m.e.s., the enzyme system which metabolizes the haloalkane, generating the free radicals responsible of many of its dangerous effects. The lipid peroxidation increases strongly in the liver of rats treated with this haloalkane; it is started by the free radicals generated by CCl_4 fission in the microsomes. The decrease of the cytochrome P_{450} and the damage to the liver endoplasmic reticulum lead to an apparent and quite interesting "paradox", shown by Ugazio et al. [7], i.e. the pre-treatment with a sublethal dose of CCl_4 protects the rats from the subsequent administration of a higher, potentially lethal dose. In fact the pretrearment impairs the hepatic microsome metabolic ability and so the subsequent haloalkane dose is less metabolized and it is unable to cause a serious liver damage and the animal death. A single, non lethal dose, of CCl_4 induces fatty liver in rats; if the treatmemt is unrepeated this degenerative process can be reversible and the hepatic tissue returns to a normal anatomic aspect and to its usual physiological functions. The demonstration that the toxicity of small doses of this haloalkane was not due to its solvent properties but was the consequence of its cleavage by the d.m.e.s underlined the importance of the interaction between the various xenobiotics, foods or drugs or air inquinants, and the living organism, human or animal. A different behaviour of the cell metabolism due to genetic factors or to different other causes, such as diseases or the assumption of various substances, can higly modify the response to xenobiotics and their effects on the health. An important step in the studies on CCl_4 toxicity was the finding that the pre-treatment of rats with antioxidants (DPPD, GSH, propyl gallate) could prevent them both from liver damage and cell death, suggesting the role of an oxidative mechanism in the development of its toxic action [8,9]. b) Lipoperoxidative effects on mitochondria. The effects of the lipid peroxidation induced by toxic compounds can be seen also in mitochondria which show a swelling and a change in ATP synthesis [9,10]. The studies with the electron microscope revealed the damage to mitochondrial components. In the first phases of the mitochondrial swelling the production of ATP can increase for an easier entry of the substrates in the organelle through the more permeable membrane, then it decreases and stops. In many intoxication both the decrease of the synthesis of ATP and the damage of the plasma membrane contribute to an increase of the Ca^{2+} influx in cells, which comes before the cell necrosis. [11]. Ca^{2+} concentration is strictly checked in cells; the

cytosolic free calcium is maintained at concentrations < 0.1 μM , which are much lower than the extracellular ones. This control is very important because an increase in Ca^{2*} activates several enzymes (ATPases, phospholipases, proteases, endonucleases) which can damage the same cell structures. c) Effects on lysosomes. The lysosomes are damaged by the attack of free radicals and by the onset of the lipid peroxidation in their membrane (12,13); so their lytic enzymes can be released in the cytoplasm. In the injured cells the intracellular pH tend to be acid; so the released lysosomal enzymes can be activated and destroy important cell components. The damage of the lysosomal membrane can lead to the enzymatic digestion of proteins, RNA, DNA and the cell dies by necrosis. The occurrence of the lipid peroxidation in lysosomes can also lead to the inactivation of their lytic enzymes if the lipoperoxidative rate is very high; Krohne et al. [14] have shown that the lipid peroxidaction end products, HNE and malonaldehyde (MDA), inactivated lysosomal cysteine proteases by covalent binding to their active center. d) Lipid peroxidation-induced changes in the nucleus. The cell nucleus has a membrane, like the other cell organelles; if the lipid peroxidation occurs in the nuclear membrane, it can cause serious damage. The nuclear importance is due to the presence of the DNA molecule; a damage to the DNA can lead to alterations in the codified proteins. If these changes involve important sites of the molecule, the protein can be no more functional. Some alterations in the DNA molecule are lethal, others lead to vital, but modified cells. Some changes in the DNA molecule can bring to the generation of transformed cells which show different changes in their morphology, metabolism and behaviour toward the near cells. The reaction of the different products of the lipid peroxidation with DNA has been extensively studied [15,16]; it can lead to the formation of adducts to DNA bases, which have profound mutagenic potential. The alterations of DNA molecule are believed to be important in the pathogenesis of cancer; a special attention has been given to the oncogenes and antioncogenes, which play an important role in regulating cell division.

4. Effects of lipid peroxidation in inflammation

The lipid peroxidation plays an important role in inflammation; in this process its presence is constant and its degree can reach high values.

Inflammation is the local response to any tissue damage. It is characterized by two main events: 1. changes in the blood flow in the microcirculation of the injured site. 2. recruitment of leukocytes, neutrophils and monocyte-macrophages; these cells phagocyte and destroy the agents of the tissue injury: bacteria, virus, parasites, dead cells, tissue debris. The leukocytes which gain the damaged tissue are activated by cytokines (IL-1, IL-6, TNF, MCP-1), which trigger the respiratory or phagocytic burst in them. This process is characterized by a strong increase of the consumption of oxygen, which is used to produce the superoxide anion ($O_2^{\bullet}$); its synthesis is catalysed by the NADPH (nicotinamide adenine dinucleotide phosphate) oxidase [17]. The NADPH oxidase is formed by a complex of proteins which are located both in the plasma membrane and in the cytoplasm in the resting neutrophil. When the neutrophil is activated by different stimuli (the phagocytosis itself, various cytokines),

the components of the NADPH oxidase assemble on the membrane of the phagosome and the enzymatic complex can reduce oxygen to superoxide anion as shown in the following reaction:

$$NADPH + O_2 \rightarrow NADP^+ + O_2^{\bullet}$$

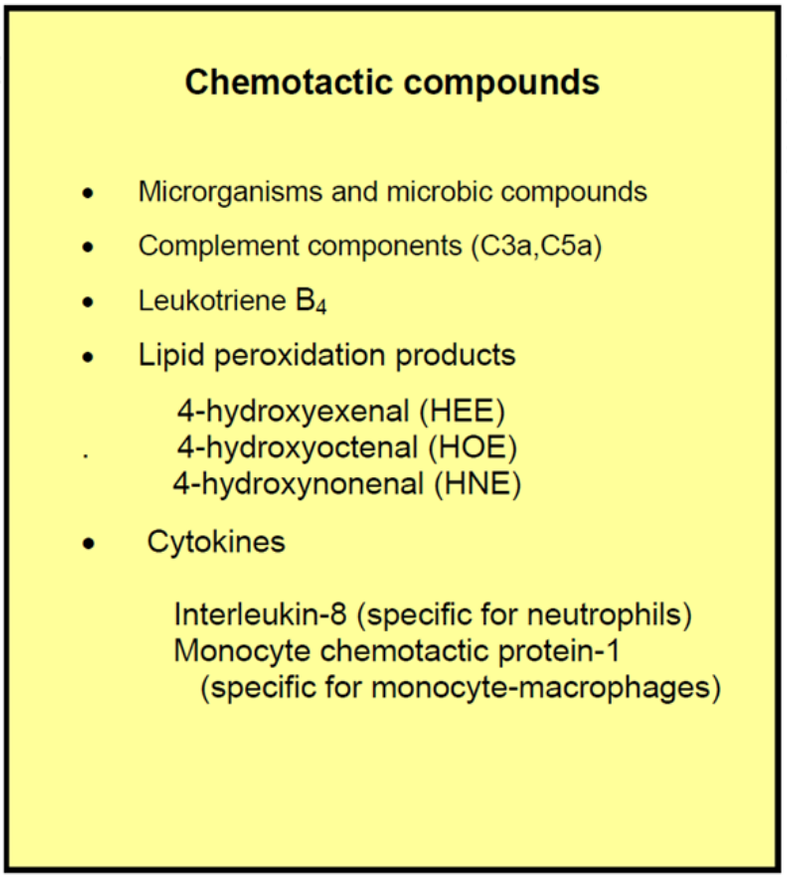

Figure 3. List of the principal chemotactic compounds.

The superoxide anion is a free radical and so it is highly reactive.Two molecules of superoxide anion can react together and form the hydrogen peroxide (H_2O_2); this molecule has a low bactericidal power and it is also used as a disinfectant in pharmacology. In the tissues the hydrogen peroxide is used in a reaction catalysed by the myeloperoxidase (MPO) to form hypochlorite ($OCl^{\bullet}$). The microbial power of the hypochlorite is very strong; furthermore it can oxidase protein and lipids and so it can trigger the lipid peroxidation. The hydrogen peroxide can also be converted to the hydroxyl radical ($OH^{\bullet}$), a free radical with a very short lifetime; in fact it reacts with the nearest molecule to acquire a more stable configuration. Both the anion superoxide and the hydroxyl radical are able to induce the lipid peroxidation and this fact explains its steady presence in inflammation. The occurrence of the lipoperoxidative process may lead to a worsening of the tissue damage, but it also contributes to the recruitment of leukocytes, both neutrophils, and monocyte-macrophages since some lipid peroxidation end products display a chemotactic power, as shown in the Figure 2. The migration of leukocytes from blood to the inflammed tissue requires several

passages [18]. Both the leukocytes and the endothelial cells need the presence of adhesion molecules on their surface to allow the leukocyte binding to the microcirculation of the damaged tissue. At first the binding is not firm and allows the leukocyte rolling on the endothelial surface; afterwards it becomes very strong and this firm adhesion is followed by the leukocyte passage outside the blood vessels to gain the site of the inflammation.

The chemotactic compounds or chemotaxins display different actions on the leukocytes. The term "chemotaxis" refers to the ability of a molecule to stimulate the oriented migration of a cell in the presence of a chemical gradient of the chemotactic compound or chemotaxin; the leukocytes have specific receptors for the different chemotaxins and move toward the site where the chemotaxins have the highest concentration. Beside this property, the chemotactic compounds display many other functions on the leukocytes: they induce the phagocyte burst, activate the adhesion molecules which are expressed on the plasmamembrane of the neutrophils, promote the synthesis of different cytokines, expecially by the macrophages.

a. Chemotactic activity of the products of the lipid peroxidation. The lipid peroxidation end product HNE has been shown to display a chemotactic power toward the polymorphonuclear leukocytes. At first this property was found by Curzio et al. (19) on rat neutrophils; the chemotactic concentrations of this aldehyde ranged from 10 μM to 0.1 μM. These doses are rather low and are devoid of any cytotoxic property. HNE chemotactic activity was initially demonstrated "in vitro" by the use of a Boyden chamber. This chamber has two compartments separated by a filter made of a mixture of cellulose esters with a pore size of 3 μ; the cells are placed in the upper chamber, the solution containing the substances to be tested in the lower one. The so mounted chamber is incubated at 37ºC for 75 min; then the chamber is removed and opened; the filter is removed, fixed in ethanol and stained with haematoxylin. The cell migration can be evaluated under the light microscope by the leading front technique. The first demonstration of HNE chemotactic power was obtained "in vitro", but afterwards it was confirmed by Schaur et al. [20] who carried on "in vivo" experimental researches. They induced an aseptic inflammation in the subcutaneous tissue of a rat leg by injecting in it some polydextrane Sephadex G-200; in control rats they inoculated Sephadex alone, while in the experimental group of rats they inoculated Sephadex together with a solution of preformed HNE. When they examinaed the histological samples obtained from the two groups of rats, they found the migration of neutrophils in both of them, but their number was much more higher around the Sephadex plus HNE. In their experimental researches the authors excluded the presence of any cytotoxic effects by the aldehyde concentrations able to stimulate the oriented migration of the neutrophils. Beside HNE, other 4-hydroxy-alkenals have been shown to display a chemotactic activity toward rat neutrophils: 4-hydroxy-2,3-hexenal(HEE) and 4-hydroxy-2,3-octenal(HOE). HOE was the most active of the lipoperoxidative end products; it could stimulate the oriented migration of neutrophils even at very low concentrations [21] between 10^{-11} and 10^{-8} M. Most chemotactic compounds can activate a phosphoinositide specific phospholipase C (PL-C) [22]; their stimulation of PL-C activity is mediated by a regulatory G protein and leads to the production of

diacylglycerol and inositol-1,4,5-tris-phosphate (Ins-P_3). The diacylglycerol activates the protein kinase C and the Ins-P_3 promotes the mobilization of Ca^{++} from intracellular stores. The well known chemotaxin N-formylmethionyl-leucyl-phenylalanine (fMLP) increases the PL-C activity of neutrophils and its action is prevented by the cell pretreatment with pertussis toxin, which ADP ribosylates the alpha subunit of some G proteins. The chemotactic 4-hydroxy-alkenals formed by the lipid peroxidation have been found to activate the PL-C [23] of rat neutrophils and a good correspondence could be found between the concentrations able to increase the PL-C activity and those which regulated the cell migration. The pretreatment of neutrophils with pertussis toxin prevented the activation of PL-C by HOE, too; this finding suggested that its mechanism of action was like that of other well known chemotaxins. This discovery of the stimulation of an enzyme activity by very low doses of 4-hydroxyalkenals represented a clean change in the evaluation of the lipoperoxidative process and of the functions of its end-products. The first experimental studies on the biological effects of the lipid peroxidation supplied a lot of proofs about the inhibition of several enzymes in tissues where the lipid peroxidation rate was stimulated [5] or about the decrease of their activity in tissue homogenates or in subcellular fractions incubated in the presence of high concentrations of HNE [24].

b. Activation of the exocytosis by 4-hydroxynonenal. HNE was found to induce the exocytosis in DMSO-differentiated HL-60 cells. [25] This human promyelocitic cell line was chosen because it could be induced to differentiate toward the granulocytic cell line and therefore it represented a good in vitro model to study the mechanism of action of a chemotactic compound, like 4-hydroxynonenal. The exocytosis was valued by measuring the secretion of ß-glucuronidase, an enzyme of the azure granules, by the cells incubated in the presence of different HNE concentrations. The exocytosis was triggered by HNE doses between 10^{-8} and 10^{-6} M, which are wholly devoid of any cytotoxic power. The lack of any effect on the cell viability was checked by measuring the release of lactate dehydrogenase (LDH) in the cells incubated at 37°C for 1 hour in the presence of different HNE concentrations; the presence of HNE between 0.01 and 1.0 μM failed to induce any increase of the enzyme loss by the cells in the incubation period [25].

c. Stimulation of IL-8 release by 4-hydroxynonenal. I recently found HNE ability to change the release of the chemokine interleukin-8 (IL-8) in DMSO–differentiated HL-60 cells [26]; the aldeyde failed to modify the intracellular concentration of IL-8, but after 30 min of incubation it began to enhance the chemokine release. The increase of IL-8 level in the cell suspensions incubated in the presence of HNE was quite slow and became remarkable only after 1 h. This fact suggested that the effects shown by the aldehyde both on the chemotaxis and on the exocytosis were not mediated through the release of IL-8.

d. 4-hydroxynonenal induced synthesis of cyclooxygenase-2. The vascular reactions of inflammation are regulated by many chemicals mediators; among them the prostaglandins influence several cell functions. The prostaglandins play an important role in inflammation; above all the PGE_2 and the PGD_2 induce vasodilation and increase the permeability of post-capillary venules. These prostaglandins are produced from

arachidonic acid by two cyclooxigenases, COX-1 and COX-2; the COX-1 is constitutively, while the COX-2 is inducible. The COX-2 js present in leukocytes and mastzellen and is induced by different mediators of inflammation. HNE has been shown to induce the synthesis of COX-2 [27] too; this finding underlines the importance of the lipid peroxidation role in inflammation.

5. Positive and negative actions of inflammation

Inflammation has many positive effects and it is considered a defensive response of the organism, but it is followed by negative aspects which may contribute to increase the tissue damage, as shown in Figure 3.

The leukocytes which reach a damaged tissue can remove the injurious agents. They can phagocyte and kill the microrganisms of an infectious disease; they also phagocyte the dead cells or the cell debris which are left in any damaged tissue.

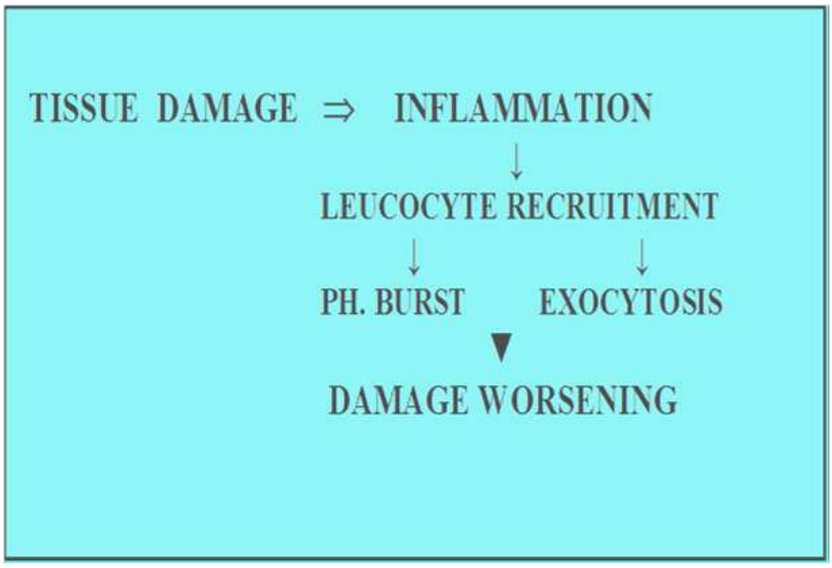

Figure 4. Main events in inflammation.

The Figure 3 underlines that the positive functions of the leukocytes are also followed by unpleasant effects, which can be caused both by the phagocytic burst and by the exocytosis. The phagocytic burst leads to the generation of free radicals and reactive oxygen species (ROS) which can diffuse outside the phagocytic cells and amplify the effects of the initial injurious agent. Moreover the induction of the lipid peroxidation by the ROS and the free radicals can worsen the tissue damage. . The exocytosis is a kind of physiological, controlled secretion of lysosomal enzymes by neutrophils and is activated by several chemotactic agent; their azurofil granules fuse with the plasma membrane and release their content in the extracellular space. In this way different lytic enzymes can diffuse in the inflammed tissue; the blood stasis which is always present in the late phases of the inflammatory process favours the lowering of pH in the damaged tissue; this fact leads to the activation of the released lysosomal enzymes and the tissue itself can be damaged.

6. Action of lipid peroxidation on atherosclerosis

Medical progress has brought good successes against many diseases in the past century. Antibiotics can win many infectious agents; the progress in surgery can correct cardiac malformations; the consequences of a vessel obstruction can be obviated by the insertion of a by pass.

In our times, when the life is becoming longer, the atherosclerosis represents a serious problem which can compromise the life of many people. The complications of the atherosclerosis are becoming the main causes of death.

Its pathological lesion is the atheroma, which is localized in the arteries of big and medium calibre: aorta, carotids, coronaries.

The atheroma is characterized by an accumulation of cholesterol and cholesterol esters both inside and outside the cells. It contains lipid-loaded cells, called foam cells. They are thought to derive from monocytes or smooth muscular cells, which have migrated in the arterial intima and have been engulfed by oxidized LDL. The lipid peroxidation plays an important role in the pathogenesis of this diffuse process through its intervent in LDL oxidation.

The modification of LDL by oxidation leads to its unregulated uptake by intimal macrophages to form foam cells[28]. In the oxidation of LDL the lipid peroxidation is stimulated and it contributes to modify their apolipoprotein. HNE, the major lipid peroxidation end product is formed also in the process of LDL oxidation and is present in the oxidized-LDL. Esterbauer et al. found that the aldehyde alone could modify the LDL. He incubated native LDL in the presence of different HNE concentrations and observed its covalent binding to the apolipoprotein B with the blockage of the epsilon-amino groups on lysine residues. Both the modification of LDL by oxidation and its modification by HNE binding were associated with an increased degradation by macrophages and a lipid loading of them.

The migration of macrophages toward the arterial intima is stimulated by chemotactic compounds, like the migration of leukocytes to a site of inflammation. The oxidized LDL have been shown to stimulate the synthesis of the monocyte chemotactic protein-1 (MCP-1) by macrophages [29]. This cytokine has a chemotactic power specific for the monocyte-macrophages; however the macrophage recruitment in the atheroma could be also favoured by the 4-hydroxyalkenals which have been found in the oxidized LDL: 4-hydrohexenal (HEE), 4-hydroxyoctenal (HOE) and 4-hydroxynonenal (HNE). These aldehydes are lipid peroxidation end products which display both a cytotoxic and a chemotactic power. They are likely to be produced by the oxidation of the LDL which have reached the intima of arteries and can contribute to the recruitment of monocyte-macrophages[30]; a direct cytotoxic effect on the foam cells of the atheroma was considered unlikely by Muller because it required higher levels of the aldehydes.

7. The lipid peroxidation role in ischemia-reperfusion.

The onset of the lipid peroxidation in a tissue requires the presence of molecular oxygen; however the ischemia can induce changes of the cell metabolism which may increase the tissue damage if the blood supply returns. This unexpected fact happens in the ischemia-reperfusion[31]. During ischemia the lack of oxygen causes the catabolism of ATP with an increased production of ipoxantine. which is an oxidable substrate for the xanthine dehydrogenase. Moreover in the ischemic tissue there is the conversion of the native xanthine dehydrogenase to a superoxide producing-oxidase; this conversion is thought to be produced by a calcium triggered protease. In the reperfusion the O_2 which reaches the tissue is transformed by the xanthine oxidase in superoxide anion; this free radical contribute to extend the tissue damage induced by the ischemia.

The tissue necrosis triggers an inflammatory process and the leukocytes which can reach the tissue in the reperfusion can worsen the tissue damage through the production of ROS and the release of lytic enzymes.

8. Conclusions

Tne lipid peroxidation can be regarded as a common process which happens in our cells. In fact low levels of the lipid peroxidation end products have been shown in tissues even in normal conditions [20]. The rate of the lipid peroxidation can be stimulated by the ROS and the free radicals which can arise also from the normal metabolism of cells.

The lipid peroxidation rate can be increased by some xenobiotics; the experimental works about the action of the haloalkane CCl_4 have been the source of the first explanations of its effects [1-3].

In any inflammation the leukocytes, above all the neutrophils and the macrophages, produce the superoxide anion and other free radicals, which can increase the lipoperoxidative rate[18]. A high degree of the lipid peroxidation is followed by some unavoidable damages to the tissue; some lesions can be reversible and can be repaired by the normal reparative process or by the aid of a pharmachological support; however a low alteration of the tissue integrity and function can follow any inflammatory event .

The aging is viewed by some authors [32] as the sum of the repeated tissue damages which occur in our life and the lipid peroxidation can take a part in them.

Another aspect of the lipid peroxidation regards its possible modulation of the normal metabolism; low concentrations of HNE, the major lipid peroxidation product, can modulate the activity of some enzymes, like the phosphoinositide-dependent phospholipase C [23] and several other enzymes [24].

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