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Review article
Pregledni članak

OXIDATIVE STRESS – CLINICAL DIAGNOSTIC SIGNIFICANCE

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Summary: Elevated free radical production and/or insufficient antioxidative defense results in cellular oxidant stress responses. Sustained and/or intense oxidative insults can overcome cell defenses resulting in accumulated damage to macromolecules, leading to loss of cell function, membrane damage, and ultimately to cell death. Oxidative stress (OS) can result from conditions including excessive physical stress, exposure to environmental pollution and xenobiotics, and smoking. Oxidative stress, as a pathophysiological mechanism, has been linked to numerous pathologies, poisonings, and the ageing process. Reactive oxygen species and reactive nitrogen species, endogenously or exogenously produced, can readily attack all classes of macromolecules (proteins, DNA, unsaturated fatty acid). The disrupted oxidative-reductive milieu proceeds via lipid peroxidation, altered antioxidative enzyme activities and depletion of non-enzymatic endogenous antioxidants, several of which can de detected in the pre-symptomatic phase of many diseases. Therefore, they could represent markers of altered metabolic and physiological homeostasis. Accordingly, from the point of view of routine clinical-diagnostic practice, it would be valuable to routinely analyze OS status parameters to earlier recognize potential disease states and provide the basis for preventative advance treatment with appropriate medicines.

Keywords: oxidative stress, free radicals, antioxidants

Kratak sadržaj: Povećano stvaranje slobodnih radikala i/ili nedovoljna antioksidativna zaštita dovodi do oksidativnog stresa (OS) u ćeliji. Produženi i/ili snažan oksidativni insult prevazilazi ćelijski antioksidativni odbrambreni kapacitet, dolazi do oštećenja makromolekula, gubi se ćelijska funkcija, oštećuju se membrane, što sve zajedno dovodi do smrti ćelije. Stanja organizma kao što su povećana fizička aktivnost, izloženost zagađenju čovekove okoline, ksenobioticima, pušenje itd. rezultiraju OS. Oksidativni stres, kao patofiziološki mehanizam, je potvrđen u brojnim patologijama, trovanjima i starenju. Reaktivne kiseonične vrste i reaktivne azotove vrste, endogenog ili egzogenog porekla, mogu lako da napadnu sve klase biomolekula (proteni, DNK, nezasićene masne kiseline). Narušen oksido-reduktivni milje, koji posreduje povećanju lipidne peroksidacije, promeni aktivnosti direktnih ili indirektnih antioksidativnih enzima, kao i smanjenom sadržaju neenzimskih antioksidanasa, može biti prepoznat u presimptomatskoj fazi brojnih bolesti. U tom smislu može biti pokazatelj izmenjenih metaboličkih i funkcionalnih zbivanja. U svakodnevnoj kliničko-dijagnostičkoj praksi analize parametara OS u biološkom materijalu bi trebalo da imaju svoje mesto, radi rane dijagnoze bolesti, prevencije i unapređivanja terapije.

Ključne reči: oksidativni stres, slobodni radikali, antioksidansi

Reactive species and oxidative stress

Reactive species (RS), a diverse group of heterogenic chemical compounds, consist of free radicals (FR) and non-radicals. Non-radical compounds, such as hydrogen peroxide (H_2O_2) and peroxynitrite ($ONOO^-$) ions, do not have unpaired electrons in their outer orbit but react similarly to FR and support red-ox reactions of RS in the body (1–3). However, FR represent the main class of RS (4). Depending on which atom is in the active centre, RS are divided into categories: reactive oxygen species (ROS); reactive nitrogen species (RNS); reactive carbon species (RCS) and reactive sulfur species (RSS) (*Table I*).

Free radicals are molecules, atoms or ions with unpaired electrons in the outer orbit, which act as oxidants due to their tendency to couple such electrons. The electrophillic properties of FR form the basis for

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Table I Reactive species.

	Radicals	Non radicals
ROS	$O_2^{\bullet -}$ superoxide anion radical $HO^{\bullet}$ hydroxyl radical $ROO^{\bullet}$ peroxyl radical $RO^{\bullet}$ alkoxyl radical $HOO^{\bullet}$ hydroperoxyl radical	H_2O_2 hydrogen peroxide HOCl hypochlorous acid O_3 ozone $^1O_2$ singlet oxygen
RNS	$NO^{\bullet}$ nitric oxide radical $NO_2^{\bullet}$ nitrogen dioxide radical	NO_2^- nitrogen dioxide anion N_2O_3 nitrogen trioxide NO_2^+ nitronium ion $ONOO^-$ peroxynitrite anion ROONO alkyl peroxynitrite NO^- (singlet) nitroxyl anion NO^+ nitrosyl cation NO_2Cl nitryl chloride
RCS	$R^{\bullet}$ alkyl radical $RO^{\bullet}$ alkoxyl radical $ROO^{\bullet}$ peroxyl radical	
RSS	$RS^{\bullet}$ thiyl radical $GS^{\bullet}$ glutathyl radical $GSSG^{\bullet -}$ diglutathione-disulfide anion radical	

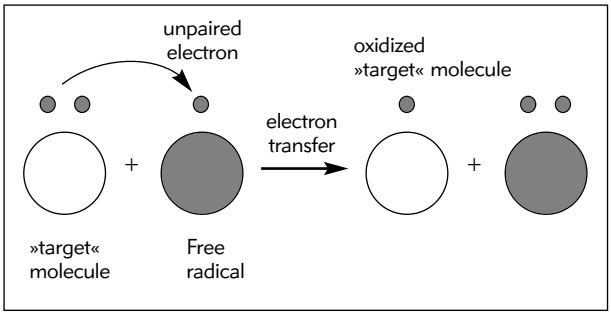

Figure 1 Mechanism of free radical effects.

their high reactivity. In reactions with FR, bio-molecules undergo oxidation and, through donation of their own electrons, they themselves become new »secondary« radicals that continue radical chain reactions and support spatial and time-dependent oxidative stress (OS) propagation and consequently lead to cell/tissue damage (1, 5).

Free radicals can be formed: 1) endogenously: a) physiologically, primarily as minor unavoidable by-products of the mitochondrial electron transport chain during cell respiration; b) through inflammatory processes, ischemia/reperfusion injury and chronic diseases such as atherosclerosis and cancer; c) via metal-catalyzed oxidation; or 2) exogenously during: a) exposure to environmental pollution and adverse conditions (ionisation, UV radiation, smoking); b) xenobiotic metabolism (6–9).

Under physiological conditions, FR concentrations are kept at low concentrations. However, their concentrations can acutely increase during numerous cell processes including erythropoesis, respiratory control and during signal transduction pathways stimulated by diverse growth factors and cytokines.

When present at high concentrations FR can directly (and indirectly) affect proteins, lipids and chromatin and can alter signal transduction pathways and gene expression. As their effects are diverse they can contribute to promote pathophysiological processes in the body.

Oxidative stress is a condition caused by an imbalance in RS production and the biological system's ability to detoxify the reactive intermediates and repair the resulting damage (10). Increased FR generation which exceeds the capacity of the antioxidative defense system (ADS) results in OS. Depletion of energy and reductive equivalents is a consequence of increased ADS activity during OS (11).

Oxidative stress often causes the disintegration of cell membranes, changes cellular morphology and function and is a prelude to cell death.

A growing body of evidence concerning oxidative damage to macromolecules by highly reactive FR underlines the contribution of OS as a component in pathophysiological mechanisms (12–14).

The involvement of RS has been identified in many pathologies (degenerative diseases, malignancy, *diabetes mellitus*, cardiovascular diseases based on atherosclerotic changes, and chemical poisoning), but also in physiological processes of ageing and apoptosis (12–17).

Antioxidative defense system

The ADS consists of several levels of protection (18):

Primary (enzymes which sequester FR: superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), glutathione reductase (GR) and non-enzymatic components (including glutathione (GSH), ascorbic acid, β-carotene, α-tocopherol) (19–23);

Secondary (specific oxidoreductase: thiol transferases, protein-ADP-ribosyltransferases and ATP and Ca^{2+} independent transferases; pigments (including melanin); and additionally some stable lipid modification such as low density lipoproteins, (LDL);

Tertiary (proteins that chelate transition metals, such as ceruloplasmin, the major copper-containing protein in plasma and apoferritin, a molecule that chelates about 4300 atoms of iron to form ferritin, a significant iron-containing protein).

The reactions forming part of the ADS are directed to different levels of cell defense with the ultimate

aim to protect cells from oxidative injury. The ADS maintains cellular homeostasis by preventing FR production, sequestering existing FR inactivating FR, providing sufficient reducing equivalents and repairing damaged cells and intracellular components (20). The main criterium for determining whether a compound is an antioxidant is if it has the ability to delay or to prevent substrate oxidation and if FR show a greater affinity to react with the potential antioxidant compared with the substrate (10).

Oxidative injury of macromolecules

Free radicals can readily attack all classes of macromolecules (proteins, DNA, unsaturated fatty acids) and have long been recognized as potential contributors to oxidative damage (21, 24, 25).

Oxidative damage of lipids

Lipid peroxidation (LP) occurs through one-electron reduction reactions between FR and unsaturated fatty acids (27, 28).

Potent FR such as $HO^{\bullet}$ and heme proteins (hemoglobin or methemoglobin) trigger LP by abstracting hydrogen and an electron from the methylene group of unsaturated fatty acids generating a lipid radical ($R^{\bullet}$) which in turn reacts with molecular oxygen (O_2) to form a lipid peroxyl radical ($ROO^{\bullet}$). The formation of LP products, considered secondary radicals, facilitates the propagation of FR chain reactions and the spreading of oxidative tissue injury. Generated LP products ($R^{\bullet}$; $RO^{\bullet}$; $ROO^{\bullet}$; ROOH) react with cell macromolecules, similarly to the primary initiating oxidant radicals ($O_2^{\bullet -}$; $HO^{\bullet}$; H_2O_2).

Target cell structures susceptible to LP are cell membranes, lipoproteins [especially low-density lipoproteins (LDL)] and molecules containing lipids.

Decomposition products of LP whether originating from the breakdown of free fatty acids or from the fatty acyl moieties of phospholipids appear to have an array of biological effects that can be related to their reactivity with proteins, DNA, and thiol compounds, and, in the case of phospholipid aldehydes, to natural agonists via cell signaling pathways. Lipid hydroperoxides may react with proteins via the addition of the peroxy radical to free amino groups, including those found in phosphatidylethanolamine (29).

Various carbonyl products arise from these decomposition reactions and are characterized as oxocompounds and alkyl or alkenyl radicals. These chain-cleavage products are, in part, comprised of reactive aldehydes, which play a significant role in the biological effects of lipid peroxidation. The major decomposition products of LP are aldehydes: malondialdehyde (MDA) and 4-hydroxynonenal (HNE). MDA originates from the breakdown of unsaturated fatty acids, predominantly arachidonic acid and when present at high concentration readily reacts with free amino groups [with the ε-amino moieties of lysine residues in apoB-100 (protein with 4536 amino acids residues) of LDL] (30). The bicyclic peroxide intermediates of linolenic and arachidonic acids give rise to MDA, commonly detected as thiobarbituric acid reacting substances (31, 32). HNE originates from the breakdown of ω-6 fatty acids (arachidonic, linoleic and linolenic acid). It is a toxic non-volatile aldehyde that electrophilically attacks thiols (Michael addition forming a glutathionyl adduct - hemiacetal rearrangement) and the ε-amino moieties of proteins (especially lysines) (33, 34). Both reactions are reversible, although reaction products with thiols are more stable. By reacting with several classes of biomolecules such as proteins, phospholipids and nucleic acid, HNE exerts multifaceted toxicity (cytotoxic, mutagenic, genotoxic) (35).

Hydroperoxide and alkoxyl radical forms of polyunsaturated fatty acids can, under appropriate conditions (for example the absence of metal catalysts), undergo intramolecular rearrangement reactions yielding epoxy-alcohols, diols, and ketones, while reactions subsequent to the rearrangement of alkoxy radicals can give rise to epoxyalcohols, ketones and alcohols (by radical disproportionation), and epoxy-ketones (36). Some of these epoxy-fatty acid products have been shown to have unique biological activities, as in the case of arachidonic acid epoxide formed by cytochrome P-450 (37). Isoprostanes are products of endocyclization of ω-6 fatty acid radical intermediates which can react with oxygen to form bicyclic endoperoxides (dioxans and dioxolanes, so-called diperoxides) bearing a variety of structures (64 isomers), or undergo elimination reactions analogous to that of prostaglandin synthase (38, 39). The formation of isoprostanes has recently been shown to be an important pathway for lipid peroxidation *in vivo* (40). In the presence of phospholipase A2 isoprostanes are released from phospholipids and enter into the body's fluidic compartments. F_2-isoprostanes are considered to be valid markers of LP and related to their chemical characteristics (stable and not dependent on daily lipid intake) with no significant inter-individual nor daily variation in its concentration and can be determined by a non-invasive method in urine or exhaled air (41). F_2-isoprostanes are similar to prostaglandin H_2 (PGH_2).

The conversion of arachidonic and linoleic acids to eicosanoids, along with other polyunsaturated fatty acids, is primarily catalyzed by various lipoxygenases (proteins with stereospecific dioxygenase activity) whose activity is influenced by the re-dox status of the cells. Enhanced lipoxygenase activity may occur through gradual accumulation of hydroperoxides via the enzymes own action, by chemicals that stimulate lipid peroxidation or by disruption of membranes from which lipoxygenase substrates are derived. Membrane

disruption permits lipoxygenase to directly oxidize unsaturated fatty acyl moieties in phospholipids or attack substrates that are released through activation of phospholipases (42, 43).

Phospholipase activation may occur during signal transduction leading to elevations in the intracellular calcium ion concentration and enzyme phosphorylation mediated by protein kinase activation (44, 45).

The release of unsaturated fatty acids from phospholipids represents a potential mechanism for phospholipase A_2-mediated lipoxygenase activation. A reverse situation for enzymatic peroxidation of membrane phospholipids followed by phospholipase-mediated degradation may also be brought about via the activation of 15-lipoxygenase (46). Excessive production of 15-lipoxygenase products has been found during septic shock (47), ischemia/reperfusion and atherosclerosis.

The propagation of LP, followed by metabolic changes, can overcome the cell's defenses. However, the extent to which LP contributes to pathologies depends on the source (endogenous or endogenous origin) that triggers the FR chain reaction.

Lipid peroxidation may be of questionable importance in biological systems, although the Fenton reaction may occur in lipid environments within membranes (48). It is likely that transition metals do not exist in normal tissues at micromolar concentrations that are required to produce sufficient $HO^{\bullet}$ to induce LP in cell membranes.

Oxidative damage of proteins

Protein modification has been observed in numerous diseases and conditions (49–51).

It is a more sensitive parameter of oxidative modification compared to LP. Protein modification specifically changes the protein's primary structure causing biological consequences such as the modification and loss of some amino acids, the formation of S-S bridges and carbonyl groups, aggregation and fragmentation, increased proteolytic sensitivity, loss of catalytic function; and changes in secondary and tertiary protein structure, which can affect viscosity and charge (52, 53).

Exposure of proteins to ROS leads to modification of amino acid side chains, conversion of proteins to higher molecular weight forms (protein-protein cross-linking) and fragmentation of polypeptide chains (54–56).

Protein modification by different RS exhibits a high degree of specificity and is divided into three categories according to chemical structure of the amino acids affected: modification of sulfur-containing amino acids, modification of aromatic and heterocyclic amino acids and modification of the aliphatic amino acids (57–60).

Modification of sulfur-containing amino acids

The two sulfur-containing amino acids sensitive to oxidative modification are cysteine and methionine.

Cysteine undergoes intra- or inter- protein disulfide cross-linked modification and may also form mixed disulfide adducts of glutathione and, in some cases, be converted to higher states of oxidation, namely, sulfinic, sulfenic, and sulfonic acid derivatives (61). Peroxynitrite converts them to S-nitrosothiol derivatives (storage and/or transfer of NO equivalents) (62–65).

Upon ROS attack methionine is converted to methionine sulfoxide (MeSOX) and occasionally to methionine sulfone (54, 55, 66–68). Disulfide forms of cysteine residues and MeSOX residues are the only ROS-mediated modifications of proteins that can be reversed. The regeneration of methionine and cysteine from their oxidized counterparts is mediated by the action of NADPH-dependent dehydrogenases.

Modification of aromatic and heterocyclic amino acids

Histidine and tryptophan residues are particularly sensitive to oxidative modification. When proteins are exposed to ionizing radiation or to high concentrations of H_2O_2 and copper, tyrosine residues are converted to 3,4-dihydroxyphenylalanine and tyrosine-tyrosine cross-linkages may be formed (69–75). In the presence of $ONOO^{-}$, tyrosine residues are converted to 3-nitrotyrosine derivatives while HOCl forms 3-chlortyrosine derivatives (76).

Modification of aliphatic amino acids

Only a few of the aliphatic amino acids are susceptible to oxidative modification. Lysine residues are converted to α-aminoadipylserine-aldehyde residues; arginine and proline residues are both converted to glutamyl semialdehyde, 4- and 5-hydroxyproline, and pyroglutamic acid; glutamyl residues are converted to oxalic acid and pyruvyl derivatives; threonine residues are converted to 2-amino-3-ketobutyric acid; and the hydrophobic amino acid residues, valine and leucine, are converted to 3-hydroxy and 3- and 4-hydroxy derivatives, respectively (55, 77, 78).

Metal-catalyzed oxidation of the side chains of lysine, arginine, proline, and threonine residues of proteins leads to the formation of protein carbonyl derivatives. However, direct oxidation of proteins is not the only way that protein carbonyl derivatives can be formed (79–81).

Oxidative damage of DNA

Nuclear DNA (nDNA) and mitochondrial DNA (mtDNA) are extremely susceptible to oxidative damage. Oxidative modification of mtDNA contributes mutations linked to myopathies, encephalomyopathies, heart diseases, late-onset diabetes, Parkinson's, Huntington's, and Alzheimer's disease, and to ageing, while oxidative damage to nDNA causes inflammation, neurodegenerative diseases, apoptosis, cancer, and ageing (82–86). The causal relationship between oxidative DNA modifications and diseases, cancer, and ageing is rarely directly documented.

The DNA antioxidative repair system includes a large number of enzymes (including DNA endonucleases, AP endonucleases, pyrimidine-hydrate-DNA glycosylase, DNA polymerases, DNA ligases), histones and FR scavengers. Defects in repair enzymes are a major risk factor for cells (87).

ROS and RNS cause base modifications (oxidation and deamination), base loss (apurinic, AP sites), single- and double-strand breaks, and cross-links in DNA. Around 100 oxidative DNA modifications have been identified (88–90). It should also be noted that ROS (and presumably RNS) not only damage DNA but may also inhibit repair activities (91). The hydroxyl radical reacts with all four DNA bases and generates a large number of characteristic products, among them 8-hydroxy-2-deoxyguanosine (8-OHdG). Nitric oxide and its congeners mainly cause DNA-deamination, but when in the $ONOO^-$ form it can also lead to a pattern of damage similar to that induced by $HO^{\bullet}$. The DNA damage profile induced by RNS may result in apoptosis (15).

Hydroxyl radicals preferentially react with DNA bases rather than with sugars and leads to modified bases, and to cleavage of the sugar-phosphate backbone of the DNA. 8-OHdG is formed in reactions of DNA with $HO^{\bullet}$, $^1O_2$, excited photosensitizers, and $ONOO^-$.

Apurinic/apyrimidinic sites (AP sites) can be formed by normal spontaneous hydrolysis and by oxidation of sugar residues. AP sites are non-instructive lesions, block DNA replication, and frequently result in deletions, because at AP sites strand breaks are readil y happen. Unlike single-strand breaks, double-strand breaks are very critical and seem to be responsible for chromosomal aberrations (92).

Involvement of oxidative stress in disease pathogenesis

Reactive species are constantly synthesized and are involved in the regulation of diverse physiological processes (93). Increased FR production and/or inadequate FR elimination by the ADS and/or non-enzymatic endogenous antioxidants results in OS. High concentrations of FR exert toxic effects and are associated with more than 100 different diseases including malignancy, autoimmune diseases, cardiovascular disease, and neurodegenerative diseases.

Oxidative stress and malignant disease

Increased ROS production is necessary but not sufficient for inducing malignancy. Furthermore, healthy cells exposed to H_2O_2 or $O_2^{\bullet -}$ upregulate the expression of genes responsible for cell growth and proliferation. Altered re-dox-dependent signaling reactions in cells can occur under conditions of increased ROS production that can ultimately contribute to cancerogenesis (mutagenesis, tumour formation and metastasis).

DNA is the most important target of highly potent ROS such as $HO^{\bullet}$. The most frequent DNA changes are base loss and formation of abasic sites (AP site), cleavage of the DNA chain and sugar modification (94). Depending on the oxidative DNA product formed the biological consequences differ. 8-hydroxy-2-deoxyguanosine (the most commonly used marker of oxidatively modified DNA produced in the reaction between purine and FR) leads to mutagenesis (95, 96). Sugar molecule damage induced by $HO^{\bullet}$ causes structural DNA damage (breakage of 5′ or 3′ phosphodiester bond). This also happens after the reaction of MDA (a terminal product of lipid peroxidation) carboxyl group and the amino group in DNA bases forming Schiff base. DNA damage also leads to mutagenesis (97, 16). Free radicals also inhibit ADP-ribosylation through NADPH depletion that in turn stimulates polyribosylation and consequently rearrangement of genetic material in DNA sequences which can be considered to be a cancerogenic phenotype (98).

Ionizing radiation causes DNA chain break and base modification, while UV radiation produces pyrimidine dimers, and as a result deletion may occur within chromosomes (99). Gamma rays induce $HO^{\bullet}$ radicals that rapidly attack all classes of biomolecules. Hydrophobic amino acids are converted to hydroxyl and hydroperoxy derivatives. The most sensitive biomarker for exposure to gamma rays is the di-tyrosyl species (100).

As the most toxic and reactive LP end product, HNE inhibits DNA synthesis, inactivates enzymes, alters cell signaling and gene expression and directly contributes to carcinogenesis (101, 102).

Some types of malignant cells (including thyroid medullary carcinomas) produce extremely high levels of ROS. Furthermore, patients suffering from malignant diseases have diminished glucose clearance thereby enhancing glycolytic activity and increasing lactate production. These pro-oxidative conditions are probably supported by the increased availability of mitochondrial energy substrates. Treatment with N-acetyl-cysteine (a precursor of glutathione synthesis) significantly

lowers proliferation indexes in patients that are at high risk for colon carcinomas or have primary colon adenomatosis polyposis. This confirms the involvement of OS in the pathogenesis of the above-mentioned diseases (103).

Oxidative stress and diabetes

Hyperglycaemia is associated with increased ROS production via multiple mechanisms. It is thought that mitochondrial complex II plays a key role in such a process.

Reduced sugars may react non-enzymatically with amino groups of proteins, as well as with lipids, including oxidative and non-oxidative rearrangements based on Millard's reaction. In reactions between reduced sugars and proteins, an unstable »Schiff base« is first produced (a fast and reversible reaction) and then the generation of final stable and irreversible products known as advanced glycosylated end products (AGE-products) (reaction of oxidative degradation and condensation, where intra-molecular rearrangement results in AGE-products generation). Glycation ($O_2^{\cdot -}$ is formed during glucose autooxidation), a common biochemical reaction in diabetics, leads to AGE-product formation that may take weeks and months to arrive completion. AGE-product binding to specific receptors (RAGE) interfers with intracellular signaling pathways and induces proinflammatory and profibrotic cell responses (104). As a consequence, an immune response occurs as well as the initiation of the prothrombotic effect (thromboxane A2 release and aggregation of thrombocytes). Hydrogen peroxide and organic peroxides are known to induce increases in intracellular calcium concentrations (105). There is evidence indicating the formation of membrane pores or ionophore-like activity and perturbations in ion pumps (106, 107) that cause calcium influx.

Rapid increases in intracellular calcium are accompanied by stimulation of protein kinase C (PKC). It is postulated that oxidation of vicinal thiols and the formation of disulfide bridges within the regulatory domain of PKC converts the enzyme to a state exhibiting calcium-and phospholipid-independent catalytic activity (108, 109). Oxidation of amino acids is involved in PKC binding to the membrane, and this oxidation may take place via peroxidation of unsaturated fatty acids in the proximity of specific amino acid residues of PKC. Further oxidation has been shown to inactivate PKC, indicating that the enzyme may undergo bimodal regulation based on the extent of oxidative modification. Reducing enzyme systems such as thioredoxin or the presence of thiol agents can inhibit modification and regulate enzyme activity (108, 110, 111).

Phospholipase A2 is a target for FR most likely via the Na+/H+ pump, Ca^{2+}, protein kinase C or receptors coupling to the activation of extra-cellular regulated protein kinase (ERK). Subsequently, arachidonic acid is released and is metabolised to endoperoxide and thromboxane. This later phase of arachidonic acid metabolism is also activated by cyclooxygenase in the presence of H_2O_2. Lipoprotein-binding phospholipase A2 (LP-PLA2) has a key role in the degradation of oxidized phospholipids and the production of lysophosphatidylcholine and oxidized fatty acids and therefore it is a very important marker of endothelial dysfunction in diabetics. There is also a correlation with C-reactive protein (CRP) concentration, which alludes to inflammation in atherosclerotically-deteriorated arteries. It is well known that the plasma concentration of CRP (acute- phase protein) increases (or decreases) by 25% or more during inflammatory disorders. CRP can rise as high as 1000-fold during inflammation.

Diabetic patients usually have high serum levels of pro-inflammatory markers [C reactive protein (CRP)] which are accurate inflammatory markers. Complications secondary to diabetes mellitus include endothelial cell dysfunction, increased aggregation of thrombocytes and activation of atherosclerosis.

MDA concentrations are elevated in diabetic patients, as well as MDA- and HNE-modified proteins (112, 113).

Several studies focussing on the role of antioxidants for the treatment of diabetics have shown promising results.

Oxidative stress and atherosclerosis

Atherosclerosis is the major cause of coronary heart disease and brain damage (114).

Oxidative stress is considered to be the dominant initiator of atherosclerosis. The role LP is clearly central to the formation of modified and atherogenic lipoproteins. Enhanced uptake and receptor-mediated delivery of the oxidized lipoproteins also provides a »targeted« means for delivering oxidized lipids and their decomposition products to intracellular sites, resulting in the signaling and expression of stress response genes, cytokines, and adhesion molecules and expression of enzymes regulating cholesterol homeostasis (115–117). These events may be evoked either directly or indirectly through the presence of LP products and, in a concerted manner, facilitate the development of an atherosclerotic lesion.

The autooxidation of hemoglobin and myoglobin represents a probable mechanism for LP involving heme normally exist in the Fe^{2+} state. Hemoglobin and myoglobin undergoes two steps of oxidation to form ferryl state (Mb-Fe^{4+}). In intermediate state, methemoglobin and metmyoglobin (Mb-Fe^{3+}) along with H_2O_2 are formed. Oxidation of heme proteins can promote atherosclerosis by facilitating oxidation from low-density lipoprotein (LDL) containing trace levels of peroxides

(118). This is supported by findings that free heme is released from injured cells in the areas of hemorrhagic plaques, iron accumulates in atherosclerotic lesions, and cells treated with heme induce the synthesis of heme oxygenase and ferritin as cytoprotectants (119, 120). These lesioned areas also contain pronounced levels of oxidatively modified lipoproteins as measured by immunospecific staining techniques (121).

The underlying basis of the pathophysiological role of OS in atherosclerosis is the induction of protein kinases including focal adhesion kinase and intracellular adhesion molecule 1, (ICAM-1) (122). Monocyte and T lymphocyte arterial wall invasion is an early event in the atherosclerotic lesion. The binding of oxidized low-density lipoproteins (oxLDL) to receptors on monocytes, macrophages and smooth muscle cells cause their activation and enhanced expression of mitochondrial superoxide dismutase (mSOD). Enhanced SOD activity contributes to elevated H_2O_2 concentration in the local environment.

The immunological colocalization of 15-lipoxygenase and oxidized LDL in endothelial cells and the subendothelial space and inhibition of LDL oxidation by lipoxygenase inhibitors provide evidence that lipoxygenase may serve as a trigger for progressive LDL oxidation. It is plausible that either specific stimuli or general tissue injury can trigger lipoxygenase activity (121, 123–125).

Esterified F2-isoprostane (a reliable oxidative stress biomarker of lipid peroxidation *in vivo*) in plasma lipoproteins clearly reflects the degree of LDL particle oxidation, as the central event of atherosclerosis, is elevated in patients with such kind of coronary disorders (126).

The formation of the atherosclerotic lesion is associated with significant macrophage apoptosis whereas its rupture is associated with endothelial cell apoptosis located in the fibrotic layer of the lesion. Phagocytes possess RAGE and after their binding AGE-products alter intracellular signaling that may be directly connected with oxLDL activation, supported by various cytokines [including tumour necrosis factor (TNF-α), interleukin 1β (IL-1β) and interferon-γ]. Additionally, angiotensin II may induce $O_2^{\cdot -}$ production in endothelial cells in the presence of cell membrane-associated nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (the major source of ROS in myocytes present in blood vessels) (127).

In addition, xanthine oxidase (XO) and myeloperoxidase (MPO) as potential sources of ROS are present in atherosclerotic plaques and the blood of patients with coronary diseases, respectively. Furthermore, in the walls of coronary arteries chlorotyrosine (formed by MPO-mediated protein oxidation by hypochloric acid) is present. Alterations in blood flow additionally contribute to tissue re-dox status.

Elevated MDA concentrations have been measured in plasma and atherosclerotic plaques of patient with coronary disease, along with complex compounds formed in the reaction between LP end products (MDA, HNE) and lysines of apolipoproteins B-100. The binding of MDA to LDL results in the formation of foam cells (128).

Oxidative stress and hypertension

Numerous experimental studies have confirmed that glutathione (GSH) depletion is associated with hypertension. Oxidative stress has been found in patients with reno-vascular hypertension (dependent on angiotensin II). In fact, angiotensin II stimulates NAD(P)H oxidase activity and upregulates SOD activity in the vascular endothelium, which is probably a compensatory reaction to increased ROS generation.

Oxidative stress and inflammatory disease

Circulatory complications during sepsis lead to inadequate oxygen delivery to tissues. Together with other cytotoxic mediators (among them ROS) massive tissue injury ensues. In the microcirculation activation of neutrophils primarily results in ROS production. Activated phagocytes defend cells against microorganism invasion through ROS production, which in turn adversely effect cells by deteriorating structure and function (129).

In addition to oxidative cell injury, nitrosative stress (NS) also contributes to overall tissue deterioration during inflammation. Nitrogen monoxide (NO), a compound with high vasoactive potential, is produced during inflammation and readily reacts with $O_2^{\cdot -}$ to form $ONOO^-$, a non-radical compound with extremely harmful pro-oxidative properties (130). Peroxynitrite can initiate lipid peroxidation, react with and deplete GSH (irreversibly inhibit mitochondrial respiratory electron transport by binding to Fe-S groups, modify DNA bases by oxidation or nitration and cleave and/or interrupt DNA strands). DNA strand breakage activates the nuclear enzyme poly(ADP-ribose)polymerase (PARP), which catalyzes degradation of nicotinamide dinucleotide (NAD) to ADP-ribose and nicotinamide. PARP then catalyzes the covalent binding of ADP-ribose to different nuclear proteins and contributes to NAD depletion in cells and a slow down of glycolysis, electron transport and production of adenosine triphosphate (ATP), processes seriously implicated in cellular dysfunction and apoptosis/necrosis.

Besides pro-inflammatory cytokines including TNF-α and IL-1, OS is one of the major inducers of nuclear transcription factor kappa B (NFκB) activity which is responsible for the transcription of genes for coding for proteins involved in inflammation (cytokines,

leukocyte-endothelial adhesion molecules and inducible nitrogen monoxide synthase (i-NOS) (131).

NFkB appears to become activated by re-dox events in cells and thus is regarded as an oxidative stress response factor (132). The ability to induce the expression of cytokine genes, along with a series of other acute response proteins in vascular cells, is shared by both oxidized LDL and fatty acid hydroperoxides. Inhibition of these responses by antioxidants is taken as evidence that the effects occur through cellular OS involving re-dox-sensitive transcriptional or post-transcriptional factors (133).

In mitochondria proteins targeted by ROS and RNS include the key enzymes for energy production (glutamate dehydrogenase, aconitase and glyceraldehyde phosphate dehydrogenase), cytochrome c oxidase-V and creatine kinase.

Oxidative stress and autoimmune diseases

Improving immune system reactivity in a pro-oxidative environment is important to impede pathogen growth and reproduction, but it also assumes risk to initiate autoimmune processes. It has been demonstrated that ROS are involved in the pathogenesis of rheumatoid arthritis at the site of inflammation. This systemic autoimmune disease is characterised by infiltration of macrophages and activated T-lymphocytes into the synovial fluid of joints. A decreased concentration of GSH was found in T-lymphocytes isolated from synovial fluid from rheumatoid arthritis patients. Low GSH alters the intracellular localization of linker for activation of T cells protein (LAT-protein) that consequently diminishes intracellular T-lymphocyte phosphorylation. Monocyte and lymphocyte migration into synovial fluid of inflammed joints is mediated by increased expression of adhesion molecules such as E-selectin (ELAM-1), vascular adhesion molecule-1 (VCAM-1), ICAM-1 and ICAM-2. It is thought that this process is a consequence of induction of cellular red-ox signaling pathways, whereas enhanced OS in synovial fluid in patients with rheumatoid arthritis is connected with a higher incidence of p53 mutation (134).

In addition, AGE-products have been detected in rheumatoid arthritis patients (135).

Oxidative stress and viral infections

An altered re-dox status is common during viral infections. The involvement of OS has been confirmed during early stage HIV infection. The turnover of cysteine (a non-essential or semi-essential amino acid) to sulfate is extremely high in patients with HIV infection. In such patients, loss of cysteine is greater than 4 g /day and such a phenomenon is observed even in the asymptotic phase of the disease. It was previously thought that the excessive cysteine loss was at the expense of extensive muscle protein catabolism (also due to muscle mass loss), but based on the ratio of sulfate/urea the interpretation was changed to that of GSH depletion. Furthermore, even in later phases of the disease massive muscle loss is observed.

Due to impairment of the immune system caused by a progressive decrease in the CD4+ T-lymphocyte population, HIV positive patients readily fall ill from different infections. The decreased number of CD4+ cells during disease progression suggests that their production is diminished, therefore cysteine supplementation is recommended.

Depletion of intracellular GSH in peripheral blood lymphocytes has been recorded in HIV positive patients. Numerous lymphocyte functions depend on intracellular GSH. Double blinded studies on HIV positive patients have convincingly demonstrated the benefits of N-acetylcysteine therapy to improve different T-lymphocyte dependent immune functions and repair natural killer (NK) cell activities to almost normal (physiological) values (122).

Stimulation of phospholipase C and chemotaxis of neutrophils by HNE are two processes occurring in patients with rheumatoid arthritis, systemic sclerosis and lupus erythematodes when its concentration is increased 3–10 fold (101, 102).

Oxidative stress and sepsis

The main inducers of OS in sepsis are activated phagocytes (polymorphonuclear cells, macrophages, eosinophils), NO generated by NOS in the vascular endothelium, Fe and Cu ions released from metaloproteins, and zones of local ischemia/reperfusion. Increased XO activity has been detected in local areas of ischemia/reperfusion in tissues of septic animals. It is well known that XO exists in two forms, as XO and xanthine dehydrogenase (XDH) and in reperfusion, XDH converts to XO which catalyses the formation of xanthine and $O_2^{\cdot -}$ from hypoxanthine (a degradation product of ATP).

Phagocytes activated by different stimuli such as lipopolysaccharides (LPS) and other pro-inflammatory mediators (TNF-α, IL-1β and IL-6) augment NADPH-oxidase and MPO activities. In activated neutrophils and phagocytes in the presence of H_2O_2 MPO catalyzes the oxidation of chlorides to hypochloric acid, leading to biochemical chain reactions for ROS production (136). During phagocytosis, throughout the process known as the »oxidative burst« oxygen depletion occurs (20 times higher than normal) and almost 90 % is converted into $O_2^{\cdot -}$ in the presence of NADPH-oxidase (as NADPH is the key electron donor) or other ROS in order to destroy microorganisms (1). Phagocytosis is the main source of ROS in sepsis (129).

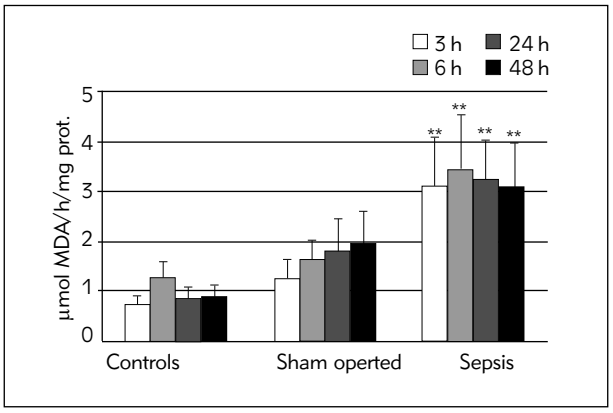

Figure 2 Lipid peroxidation index in brain capillaries of septic Wistar rats.
** statistical significance compared to controls (sham-operated animals), $p<0.01$

Increased 15-lipoxygenase activity (leading to leukotriene production) is observed in reperfusion of ischemic tissues (137). Attenuation of ischemia/reperfusion injury by lipoxygenase inhibitors and antioxidants indicates the important role of lipoxygenase-mediated reactions in the common pathological condition.

However, decreased levels of antioxidants (ascorbate, α-tocopherol, GSH) and vitamin A in plasma of septic patients clearly reflect the involvement of OS.

It is possible to detect OS in the central nervous system (CNS) at an early stage of sepsis. We have detected LP in brain capillaries isolated from rats induced by a modified method of cecal ligation and perforation (*Figure 2*) (138).

Oxidative stress and ischemia/ reperfusion

Ischemia and reperfusion are pathophysiological events often studied to understand aspects of reductive/oxidative stress (139). Reperfusion injury after myocardial infarction, stroke or organ transplantation is a well-known complication of insufficient tissue reoxygenation. In energy exhausted cells, in ischemia/reperfusion domains, where significant ATP depletion occurs, adenosine is degraded to hypoxanthine which further undergoes oxidation to xanthine and $O_2^{\cdot -}$, catalyzed by XO in the presence of NAD+ (an electron acceptor). The $O_2^{\cdot -}$ produced, indicates that OS mediates such events. Oxidatively modified proteins have been detected in ischemia/reperfusion areas (50–53, 140, 141).

Neutrophils are the major effectors during reperfusion injury. It has been demonstrated that antioxidants improve leukocyte adhesion and decrease post-ischemia myocardial injury. Experimentally induced ischemia/reperfusion in the rat heart is connected with activation of red-ox susceptive transcription factors responsible for the inflammatory response and apoptosis in injured tissue (142).

Systemic ischemia/reperfusion is observed in patients with the obstructive syndrome »sleep apnoea« (repeated episodes of apnoea or hypopnoea during sleeping). The involvement of ROS in cardiovascular complications in patients with »sleep apnoea« has been confirmed by measuring high $O_2^{\cdot -}$ concentrations in peripheral blood neutrophils. In addition, increased expression of adhesion molecules, ICAM-1 and VCAM-1 has also been found in these patients. Hypertension, along with other cadiovascular diseases, is very common in such patients.

Oxidative stress and brain diseases

Due to high oxygen demands, intense oxidative phosphorylation activity and high concentrations of unsaturated fatty acids (UFA) neuronal tissue is especially vulnerable to oxidative injury (143). An increased level of MDA has been found in plasma and cerebrospinal liquid in patients that experienced a reversible transient ischemic attack (TIA) (often colloquially referred to as »mini stroke«) and a stroke (144). Due to high Fe ion concentrations as well high metabolic turn over of dopamine (one of the bi-products being $O_2^{\cdot -}$) basal ganglia are particularly susceptible to oxidative damage (145).

The contribution of OS to the pathogenesis of Parkinson's disease has been confirmed by numerous experimental and clinical studies [10]. Elevated MDA concentrations and changed in SOD activity have been found in patients with Parkinson's and Alzheimer's diseases (146, 147).

In an experimental study concerning the development of inheritable Huntington's disease we have shown excitotoxicity effects (the pathological process by which neurons are damaged and killed by excitatory neurotransmitter receptor over-activation) by OS and NS in basal ganglia (148).

Furthermore, in an experimental model of Alzheimer's disease we have reported that the harmful effect of aluminium intoxication is mediated by ROS and results in brain tissue injury typical of Alzheimer's disease (147).

SOD over-expression causes H_2O_2 production which can be a precursor of toxic $HO^{\cdot}$ species. There is evidence to suggest that this process could be present in Down's syndrome sufferers. Additionally, with respect to the neurotoxic effects of pesticides (paraquat and diquat) in rats we have reported OS as a key damaging process targeting vulnerable brain regions (149).

Oxidative stress and unaccustomed body exercise

Increased ROS production has been found after extreme muscular activity. It has been shown that unaccustomed exercise is known to result in significant damage to skeletal muscle in both trained and untrained subjects. Exercise in excess (an acute increase in volume, intensity, and/or mode) of that to which a muscle has become adapted can be termed acute unaccustomed stress (AUS). The resulting damage to the muscle can be structural and/or metabolic. Although reduced metabolic function after AUS has been demonstrated, the underlying causes remain unclear (150).

A decreased reduced/oxidized glutathione ratio (GSH/GSSH) together with a two-fold increase in ROS concentration in skeletal muscle and liver after AUS bouts (due to enhanced oxygen demands and increased XO activity) has been observed in plasma and erythrocytes. Loss of muscular oxidative capacity and metabolic changes occur in an athlete's muscle after AUS bouts. Sustained OS can have adverse effects on mitochondrial function after long duration exercise bouts (151).

A significantly lowered GSH/GSSH and increased MDA level has been found in arterial blood of patients with obstructive lung disease after unaccustomed exercise. Improvement was observed after treatment with alopurinol, a potent inhibitor of XO. In addition, the consumption of N-acetylcysteine improves muscle condition after AUS bouts, which confirms alteration of the GSH status.

Oxidative stress and poisoning by bypiridyles

Numerous xenobiotics (including environmental pollutants, X- and UV- rays, medicines, industrial solvents, toxic metals and smoking) exert their toxicity via FR production (1–3, 6, 7). Bypridyles are fine examples of chemical agents that are pro-oxidative in nature.

Paraquat (PQ) and diquat (DQ) are quaternary nitrogen compounds and contact herbicides widely used in agriculture. They are extremely toxic to humans and animals by all routes of exposure such as inhalation and digestion. PQ causes progressive lung and kidney failure resulting in convulsions, uncoordination and death due to respiratory failure. DQ toxicity is mediated via the liver and kidney. These herbicides have been classified as possible human carcinogens.

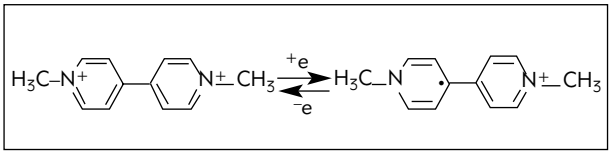

Figure 3 Stability of $PQ^{\cdot +}$ due to conjugated double bonds in the pyridine ring and the presence of quaternary nitrogen in the second pyridine ring.

Both paraquat and DQ toxicity is mediated by FR production during their re-dox metabolism.

In the presence of NADPH and molecular oxygen, PQ^{2+} (the di-cation form of PQ) undergoes one-electron reduction to form the stable PQ-radical ($PQ^{\cdot +}$) and $O_2^{\cdot -}$ (*Figure 3*) (152). $O_2^{\cdot -}$ further dismutates into H_2O_2, by SOD or via a spontaneous reaction. Chain radical reactions are triggered that induce oxidative tissue injury which is an underlying mechanism of PQ toxicity.

The ROS generated provoke the development of OS in target tissues. In our experimental studies on rats intrastriatally poisoned with PQ and DQ we demonstrated that both herbicides induced oxidative damage of neuronal tissues (*Figure 4*). Oxidative stress status parameters ($O_2^{\cdot -}$, MDA, GSH, SOD and GSH-Px) were determined in three vulnerable brain regions (striatum, cortex and hippocampus) after 30 min, 24 h and 7 days, by standard analytical methods (153).

Reversible Parkinson's-like symptoms were observed immediately after poisoning with PQ. A high degree of similarity between PQ and MPTP (1-methyl 4-phenyl 1,2,3,6-tetrahydropyridine) supports the hypothesis that the obtained effects are analogous (Figures 3 and 5). It is well known from the literature that MPTP, a by-product of an illicit narcotic drug, is a neurotoxin that causes permanent symptoms of Parkinson's disease affecting dopaminergic neurons in the Substatia Nigra of the brain.

The results from our experiments indicate that the most obvious mechanisms of the neurotoxic effects of the herbicides were due to LP and increased GSH-Px activity in the striatum. This clearly proves the notion concerning induced OS and neuronal damage.

Conclusion

Oxidative stress as a pathophysiological mechanism has attracted the attention of researchers since the 1950s. Perturbed red-ox homeostasis has been confirmed in more than 100 diseases. The toxic effects of excessively produced FR result in oxidative cell injury, thus finding appropriate OS biomarkers is of great significance for clinical laboratory diagnostics (155, 156).

Better insight into the pathophysiological mechanism(s) of numerous diseases could be achieved if clinical laboratories implement OS diagnostic biomarker measurements. Even in asymptotic phases of diseases a perturbed red-ox status can be observed. Nowadays, the determination and monitoring of OS status parameters is very important for clinical diagnostics as well as for the evaluation of treatment efficacy.

The consumption of antioxidants has provided encouraging results in the prevention and treatment of many diseases. The discovery of novel antioxidants is a

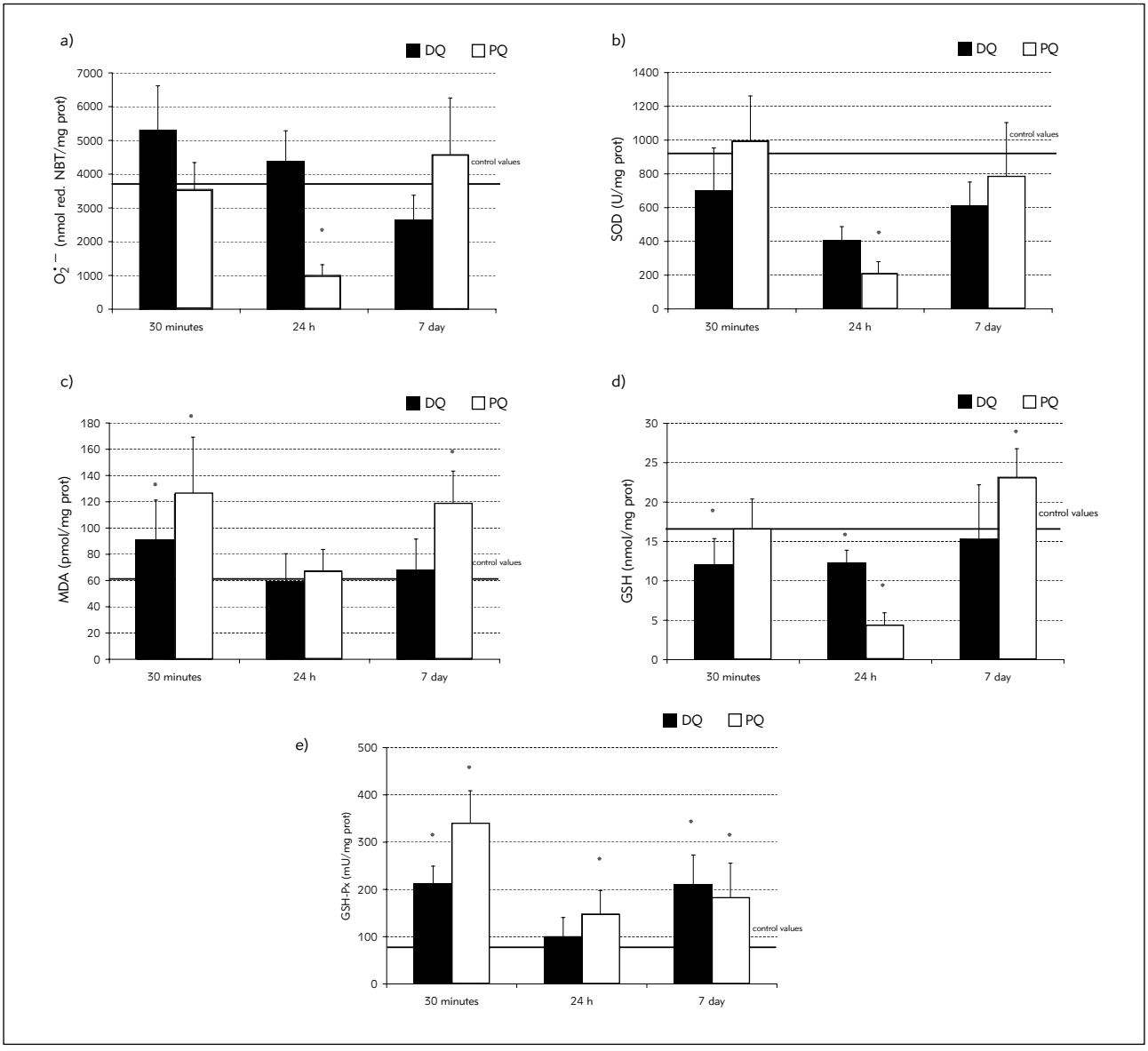

Figure 4 Oxidative stress parameters in the striatum of Wistar rats intrastriatally poisoned with paraquat and diquat. a) Concentration of superoxide anion radical in the striatum of Wistar rats intrastriatally poisoned paraquat and diquat; b)Activity of superooxide in the striatum of Wistar rats intrastriatally poisoned paraquat and diquat; c) Lipid peroxidation in the striatum of Wistar rats intrastriatally poisoned paraquat and diquat; d) Concentration of glutathione in the striatum of Wistar rats intrastriatally poisoned paraquat and diquat; e) Activity of glutathione perooxidase in the striatum of Wistar rats intrastriatally poisoned paraquat and diquat. Statistical significance is indicated for $p<0.05$. Control values are indicated as the bold horizontal line within the panels. The experiment was conducted on Wistar rats of both sexes (11 weeks old with an average body mass 250 g). Each experimental group consisted of 8 animals placed in one cage with free access to food and water. On the seventh day before the experiment the animals were adjusted to the experimental conditions including temperature (23 ± 2 °C) and a circadian ratio of light and dark 11:13 (154). Before poisoning Wistar rats were anesthetized intraperitoneally with sodium pentobarbital (40.5 mg/kg TM). The control group of animals were intrastriatally treated with 10 μL of physiological saline and the poisoned groups with PQ and DQ at a dose of 50 mg/kg (2.5 μg/10 μL).

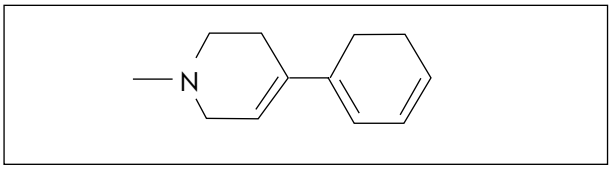

Figure 5 Chemical structure of MPTP.

key objective of many researchers in the field of prevention and disease treatments (157–161).

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