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Oxidative Stress in Uremia: Nature, Mechanisms, and Potential Consequences

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Oxidative stress has emerged as a constant feature of chronic renal failure (CRF). The presence of oxidative stress in CRF is evidenced by an overabundance of lipid, carbohydrate, and protein oxidation products in the plasma and tissues of uremic patients and animals. We recently have shown that oxidative stress in CRF animals is associated with and, in part, owing to up-regulation of superoxide-producing enzyme, nicotinamide-adenine dinucleotide phosphate (NAD(P)H) oxidase, and down-regulation of superoxide dismutase (SOD). The functional significance of these findings was confirmed by favorable response to administration of the cell-permeable SOD-mimetic agent, tempol, in CRF rats. Oxidative stress in CRF plays an important role in the pathogenesis of the associated hypertension (oxidation of NO and arachidonic acid and vascular remodeling), cardiovascular disease (oxidation of lipoproteins, atherogenesis), neurologic disorders (nitration of brain proteins, oxidation of myelin), anemia (reduction of erythrocyte lifespan), inflammation (nuclear factor κ B activation), fibrosis, apoptosis, and accelerated aging. The CRF-induced oxidative stress is aggravated by diabetes, uncontrolled hypertension, and autoimmune diseases, which independently increase production of reactive oxygen intermediates, and frequently are associated with CRF. In addition, dialysis treatment (blood interaction with dialyzer membrane and dialysate impurities), acute and chronic infections (blood access infection, hepatitis, and so forth), and excessive parenteral iron administration intensify CRF-associated oxidative stress and its adverse consequences in patients with end-stage renal disease. The problem is compounded by limited intake of fresh fruits and vegetables (K^+ restriction), which contain numerous natural phytochemicals and antioxidant vitamins.

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Oxidative stress is a common feature and a major mediator of various complications of chronic renal failure (CRF). This article provides a brief overview of the nature, mechanism, consequences, and potential treatment of CRF-associated oxidative stress.

Generation and Metabolism of Reactive Oxygen Species

Conversion of molecular oxygen to water involves acquisition of 4 electrons ($O_2 + 4H \rightarrow 2H_2O$), which occurs in a single step for the great majority of the oxygen consumed in the body. However, for a small fraction (2% to 5%) of the O_2 consumed, this process occurs with the transfer of one electron at a time, leading to the generation of highly reactive, intermediary, oxygen metabolites known as reactive oxygen species (ROS). Normally, ROS play an important role in numerous biologic functions as signal molecules. In addition, generation of ROS by activated leukocytes and macrophages plays a critical part in host defense against invading pathogens. ROS can attack, modify, and denature functional and structural molecules causing cytotoxicity, tissue damage, and dysfunction. In addition, ROS can promote apoptosis, fibrosis, cell proliferation, and inflammation by triggering different signal transduction pathways and transcription factors (eg, nuclear factor κ B).

ROS are produced as byproducts of O_2 metabolism by mitochondrial cytochrome oxidase, nicotinamide adenine dinucleotide (phosphate) [NAD(P)] oxidase family, xanthine oxidase, lipooxygenase, cyclooxygenase, heme oxygenase,

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cytochrome P-450 enzymes, nitric oxide synthase (in uncoupled state or in the presence of cofactor/substrate depletion), and various other oxidase enzymes.

Under normal conditions, ROS produced in the course of metabolism are contained by the antioxidant defense system consisting of antioxidant enzymes and endogenous and dietary antioxidants. Increased production of ROS and/or impaired antioxidant system leads to oxidative stress in which uncontained ROS cause tissue damage and dysfunction. Superoxide ($O_2°$) is a highly reactive cytotoxic ROS that is generated from a one-electron (e^-) reduction of molecular oxygen ($O_2 + e^- \rightarrow O_2°$). It is converted to hydrogen peroxide by superoxide dismutase (SOD), which consist of mitochondrial SOD, cytoplasmic SOD, and extracellular SOD: ($O_2° + O_2° + 2H^+ \xrightarrow{SOD} H_2O_2 + O_2$). Hydrogen peroxide is, in turn, reduced to water by either catalase ($2H_2O_2 \xrightarrow{CAT} 2H_2O + O_2$), or the selenoprotein enzyme, glutathione peroxidase, which uses glutathione as a hydrogen donor (H_2O_2 + 2 glutathione $\xrightarrow{\text{glutathione peroxidase}} 2H_2O + GS – SG$).

Although under normal conditions H_2O_2 is converted safely to water, under abnormal conditions H_2O_2 serves as a substrate for the generation of several highly cytotoxic byproducts. For instance, in the presence of transition metals (iron and copper) or excess $O_2°$, H_2O_2 is converted to hydroxyl radical (.OH), which is the most cytotoxic ROS known: $H_2O_2 + Fe^{2+} \rightarrow .OH + OH^- + Fe^{3+}$, $H_2O_2 + O_2° \rightarrow .OH + OH^- + O_2$

These reactions show the potential risk for transition metal overload as a mediator of oxidative stress. H_2O_2 also serves as the substrate for phagocyte myeloperoxidase, generating hypochlorous acid ($H_2O_2 + Cl^- + H^+ \xrightarrow{\text{myeloperoxidase}} HOCl + H_2O$), which can denature various molecules, especially proteins. For example, interaction of tyrosine residues with HOCl leads to the formation of 3-chlorotyrosine and dityrosine, which are found in atherosclerotic plaques and oxidized low-density lipoprotein (LDL).[1,2] The other biochemical reaction of interest is interaction of ROS, particularly $O_2°$, with nitric oxide (NO), which can lead to diminished NO availability and formation of peroxynitrite ($ONOO^-$), a highly cytotoxic reactive nitrogen species ($NO + O_2° \rightarrow ONOO^-$). Peroxynitrite can cause lipid peroxidation, DNA damage, and protein nitration. For example, interaction of peroxynitrite with the tyrosine residues results in the formation of nitrotyrosine, which can modify the function and structure of many proteins and interfere with signal transduction pathways involving tyrosine phosphorylation.

Markers of Oxidative Stress in CRF

Because of their extreme instability, it is difficult to detect ROS directly in vivo. Instead, the oxidative burden in humans and animals generally is assessed by measuring the stable byproducts of ROS interactions with bimolecules, such as lipids, carbohydrates, proteins, nucleic acids, and NO. Numerous studies have shown marked increases of various lipid peroxidation products in uremic humans and animals. For instance, plasma concentrations of free and phospholipid-bound F_2 isoprostanes, isolevuglandins, oxidized LDL, 4-hydroxy-2-nonenal, and malondialdehyde, as well as breath ethane, are increased significantly in CRF.[3-8] Likewise, byproducts of protein/amino acid oxidation, such as 3-chlorothyrosine, dithyrosine, nitrotyrosine, oxidized thiols, carbonylation products, advanced oxidative protein products, and L-isoaspartyl residues are increased in uremia. Oxidation of the thiol groups in proteins and small molecular thiols by ROS is of particular importance. This is because increased oxidation of thiols profoundly affects structure and function of many proteins and impairs the intracellular and extracellular redox state, as well as ROS scavenging capacity. Several studies have shown marked reductions of the plasma glutathione concentration and glutathione peroxidase activity, as well as a marked increase in the ratios of oxidized to reduced glutathione, cysteine, and homocysteine in CRF patients.[9-11]

Oxidation of alcohol groups, amino groups, and double carbon bonds in carbohydrates, amino acids, and unsaturated fatty acids by ROS leads to the formation of reactive aldehydes, which can be identified by the presence of carbonyl (C = 0) groups. One of the well-known consequences of these carbonylation reactions is the formation of the advanced glycooxidation end products (AGE) resulting from irreversible binding of the reactive carbonyl groups of oxidized carbohydrates to the free amino groups of amino acid residues of plasma and tissue proteins. The plasma concentration of reactive carbonyl products and AGE are increased markedly in CRF patients.[12-15]

Taken together, these observations provide irrefutable evidence for the presence of oxidative stress in CRF humans and animals. In addition to serving as markers of oxidative stress, many of the oxidation byproducts noted earlier, such as lipid peroxidation products, oxidized LDL, reactive carbonyl compounds, AGE, and oxidized thiol compounds, substantially contribute to the pathogenesis of inflammation, cardiovascular, and other complications of uremia.

Mechanisms of Oxidative Stress in CRF

Oxidative stress can occur as a result of either excess ROS generation and/or impaired antioxidant capacity. Studies in CRF humans have been limited to the relevant measurements in blood samples and have revealed significant decreases in blood levels of antioxidant enzymes, glutathione, and ascorbic acid, as well as protein oxidation patterns consistent with leukocyte myeloperoxidase-mediated events.[3]

Increased ROS generation in CRF patients has been attributed to the effects of endogenous and exogenous uremic toxins, angiotensin II, blood-dialyzer membrane interaction, influx of endotoxin fragments from dialysate, reaction to catheters and arteriovenous grafts, chronic infections, iron overload, and the underlying immunologic or metabolic disorders such as diabetes. In addition, byproducts of oxidative stress (eg, AGE, oxidized LDL, and lipoperoxides) augment oxidative stress and inflammation via activation of macro-

phages. Because of the inherent limitation of the clinical studies, it has been difficult to dissect the role of renal insufficiency per se from those of the underlying diseases, comorbid conditions, and therapeutic interventions in humans. Moreover, in-depth investigation of the molecular basis of oxidative stress, which requires access to the internal organs of interest, is impossible in CRF patients. To address these issues, we explored oxidative stress in CRF induced by 5/6 nephrectomy in genetically normal otherwise intact animals. The results of these studies are included in this article.

NAD(P)H oxidase has emerged as a major source of ROS production, not only in leukocytes and macrophages but also in renal and cardiovascular tissues. In fact, NAD(P)H oxidase and its newly identified isoforms, NOX-1 and renox, are expressed in endothelial cells, vascular smooth muscle cells, and renal tubular epithelial cells, respectively. In a recent study, we found significant up-regulation of NAD(P)H oxidase coupled with marked down-regulations of cytoplasmic SOD and mitochondrial SOD in the remnant kidney and liver of CRF rats.[16] These abnormalities can result in increased production and depressed dismutation of O_2° in CRF. This assumption was substantiated by the accumulation of nitrotyrosine (a footprint of the ROS-NO–tyrosine interaction) and by the favorable response to administration of the cell-permeable SOD-mimetic drug, tempol, in the CRF animals.[16] In confirmation of our earlier study,[17] xanthine oxidase activity was decreased significantly in CRF animals, thus excluding xanthine oxidase as a cause of the associated oxidative stress. It is of interest that activation of the angiotensin receptor type-1 receptor by angiotensin II results in up-regulation/activation of NAD(P)H oxidase.[18] Consequently, angiotensin-converting enzyme inhibitors and AT-1 receptor blockers can serve as specific antioxidants in CRF animals and humans. This phenomenon is in part responsible for the superiority of these agents (compared with other equally potent antihypertensive drugs) in the treatment of chronic renal disease.

As noted earlier, blood SOD, catalase, glutathione peroxidase, and glutathione levels are decreased markedly in CRF patients.[3] Therefore, overproduction of ROS and antioxidant depletion work in concert to produce oxidative stress in CRF.

Consequences of Oxidative Stress in CRF

Oxidative stress is a potential mediator of cardiovascular, neurologic, and several other complications of CRF.[3] For example, oxidative stress is involved in the pathogenesis of hypertension,[4] endothelial dysfunction,[20] neurologic disorders,[21] shortened erythrocyte lifespan,[22-25] atherosclerosis, and inflammation in CRF.[3]

Role of Oxidative Stress in CRF-Induced Hypertension

Oxidative stress can cause hypertension by promoting ROS-mediated inactivation of NO, generation of vasoconstrictive isoprostanes (oxidation of arachidonic acid), and cardiovascular remodeling. In an earlier study designed to explore the role of oxidative stress in the pathogenesis of uremic hypertension, we found parallel increases in arterial pressure and oxidative stress markers together with a marked decrease in NO availability after induction of CRF by 5/6 nephrectomy in rats. Antioxidant therapy (lazaroid compound) alleviated oxidative stress, attenuated hypertension, and restored NO availability in CRF animals. Oxidative stress reappeared, blood pressure increased, and NO availability decreased within 2 weeks after discontinuation of antioxidant therapy. Together these observations clearly showed the causal role of oxidative stress in the pathogenesis of uremic hypertension.[4] In a subsequent study,[19] we showed that functional NO deficiency in CRF is in part caused by NO inactivation by ROS and sequestration of NO as nitrated proteins throughout the body. The study further showed that both hypertension and NO sequestration could be attenuated by antioxidant therapy with high doses of vitamin E.[19] In addition to promoting NO inactivation, oxidative stress can decrease NO production and augment ROS generation by uncoupling NO synthases (NOS) and depleting the NOS cofactor tetrahydrobiopterin. These events favor generation of O_2° instead of NO by NOS. The effect of oxidative stress on NO metabolism is compounded by down-regulation of NOS expression in the diseased kidney and cardiovascular system in CRF.[26]

Role of Oxidative Stress in CRF-Induced Endothelial Dysfunction

NO is a major mediator of endothelium-dependent vasorelaxation. Accordingly, the combination of NO inactivation by ROS and depressed NO biosynthesis are largely responsible for the endothelial dysfunction in CRF. This supposition recently was confirmed by Hasdan et al,[20] who showed that pretreatment with heparin-binding SOD restored blood flow response to acetylcholine in the mesenteric arteries of CRF animals.

Role of Oxidative/Nitrosative Stress in Brain Disorders in CRF

Encephalopathy and peripheral neuropathy are well-known complications of CRF. Because of overabundance of oxidation-prone polyunsaturated fatty acids and several other reasons, the neuronal tissues are highly vulnerable to oxidative stress. In addition to inflicting direct neurotoxicity via peroxidation of phospholipid membranes, ROS cause excitotoxicity by facilitating glutamate release. This leads to activation of NMDA and non-NMDA receptors, which results in a severe increase in intracellular Ca^{2+} levels, activation of neuronal NOS, formation of peroxynitrite, protein nitration, and mitochondrial damage, culminating in neuronal injury or death. Therefore, oxidative stress potentially can contribute to the neurologic disorders in CRF. In fact, in an earlier study,[21] we showed overabundance of nitrotyrosine in the axons, dendrites, and somata of neurons in the cerebral cortex of uremic rats and its reversal by antioxidant therapy. It is of note that tyrosine nitration in the uremic brain may result

in excitotoxicity via direct activation of NMDA and non-NMDA receptors by nitrotyrosine.

Thus, animal studies have provided convincing evidence that CRF, per se, in the absence of any underlying systemic disorder, causes oxidative stress. These studies have documented further the role of increased production of O_2° by NAD(P)H oxidase (but not xanthine oxidase) and decreased O_2° dismutation by SOD in the pathogenesis of CRF-induced oxidative stress. Finally, the animal studies cited earlier have substantiated the contribution of oxidative stress to the pathogenesis of hypertension, endothelial dysfunction, and neurologic complications of CRF. Moreover, these studies have provided the rationale for the use of antioxidants and renin-angiotensin blockers in CRF.

Role of Oxidative Stress in CRF-Associated Anemia

Anemia of CRF is caused primarily by a combination of depressed erythropoiesis (erythropoietin deficiency, impaired iron use, 2° hyperparathyroidism) and a shortened erythrocyte lifespan. The latter largely is caused by oxidative stress via oxidation of cell membrane phospholipids, glutathione depletion, and altered intracellular redox state. In fact, antioxidant therapy has been shown to improve anemia in CRF humans and animals, and reduce the required dosage of recombinant erythropoietin in dialysis-dependent patients.[16,27-30]

Oxidative Stress, Inflammation, and Atherogenesis in CRF

Inflammation is a common feature and a major predictor of cardiovascular mortality in CRF patients.[31,32] Inflammation in CRF patients is evidenced by an increase of plasma concentration of acute-phase reactants, such as C-reactive protein. Inflammation and oxidative stress are interrelated intimately because oxidative stress can cause inflammation and inflammation can cause oxidative stress. For example, oxidative stress results in the activation of the redox-sensitive transcription factor nuclear factor κ B, which leads to the generation of proinflammatory cytokines and activation of leukocytes and macrophages. In addition, byproducts of oxidative stress such as AGE, lipoperoxides, and oxidized LDL can promote inflammation by activating leukocytes and macrophages. Conversely, inflammation is accompanied by production and release of ROS and other reactive species by inflammatory cells, leading to oxidative and nitrosative stress. The interdependence of the 2 phenomena is reflected by close positive correlations between markers of oxidative stress with those of inflammation, particularly C-reactive protein in CRF patients.[3] Thus, inflammation and oxidative stress are involved in a spiraling vicious cycle that contributes to cardiovascular and other complications of CRF. These observations support the potential usefulness of antioxidant therapy and the identification and correction of treatable sources of inflammation in CRF patients.

Treatment of Oxidative Stress in CRF

The treatment of oxidative stress should include 2 distinct strategies, as described.

Identification of the Source and Control of Production of ROS

Given the role of angiotensin II in ROS generation, the blockade of angiotensin II production or action represents a specific step in the management of oxidative stress in chronic kidney disease. In addition, the identification and treatment of infections, removal of vascular catheters or failed grafts, and substitution of bioincompatible with biocompatible dialyzers are essential in alleviating inflammation and excess ROS generation. Moreover, adequate hypertension and uremia control are critical steps in mitigating NAD(P)H oxidase activity and ROS generation in patients with end-stage renal disease. Finally, satisfactory control of hyperglycemia and hyperlipidemia, when present, and prevention or correction of iron overload are essential for successful management of oxidative stress in this population because these conditions promote ROS generation and impair the antioxidant defense system. The well-known benefit of the earlier-described measures in patients and animals with different stages of renal disease is, in part, owing to their ability to attenuate local and systemic generation of ROS. In addition, the use of oral adsorbents (eg, AST-120) and a high-fiber diet may help to reduce absorption of bacterial byproducts and uremic toxins that promote oxidative stress and inflammation.

Use of Antioxidant Regimens

In addition to measures directed at decreasing production of ROS, judicious use of antioxidant supplements should be considered in CRF patients. This is based on several observations pointing to antioxidant depletion in CRF. First, as noted earlier, advanced CRF results in the reduction of the endogenous antioxidant enzymes (SOD, catalase, and glutathione peroxidase), glutathione, free thiol groups, as well as high-density lipoprotein, which is a potent antioxidant. Second, intake of fresh fruits and vegetables, which contain numerous antioxidants, is limited by either anorexia or dietary restriction (to reduce potassium and fluid intake) in CRF patients, and, third, significant losses of water-soluble antioxidants occur during dialysis in end-stage renal disease patients.

Vitamins E and C are potent and readily available antioxidants that have been considered for the treatment of oxidative stress in CRF. However, when used in large quantities, vitamin C potentially can exacerbate oxidative stress by becoming a prooxidant and by catalyzing conversion of Fe^{3+} to Fe^{2+}, which favors formation of hydroxyl radical.[33] Therefore, large doses of vitamin C should be avoided in CRF patients. However, as reviewed by Himmelfarb et al,[3] vitamin E supplementation generally has been associated with amelioration of oxidative stress and anemia in end-stage renal disease patients. In addition, according to a recent study,

daily administration of vitamin E (800 IU) resulted in a significant decrease of myocardial infarction and other cardiovascular complications (but not overall mortality) in end-stage renal disease patients.[34] Similarly, we have found amelioration of oxidative stress and hypertension and improved NO availability in CRF rats treated with high doses of vitamin E.[19] Although the available data point to the beneficial effects of vitamin E, I believe that the ideal approach to the management of oxidative stress in CRF remains elusive and awaits in-depth investigation of the ROS-generating and antioxidant systems to identify specific defects and formulate specific remedies. In the meantime, I believe that when possible, a diet containing adequate amounts of fresh fruits and vegetables, which provide a well-balanced combination of numerous antioxidants and many useful phytochemicals, should be encouraged.

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