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Role of oxidative stress in the pathogenesis of hypertension

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Acronyms
ACE: angiotensin-converting enzyme
DNA: deoxyribonucleic acid
eNOS: endothelial NOS
HT: hypertension
NADPH: nicotinamide adenine dinucleotide phosphate
NO: nitric oxide
NOS: nitric oxide synthase
OS: oxidative stress
ROS: reactive oxygen species
SOD: superoxide dismutase
VSMC: vascular smooth muscle cells

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ABSTRACT
The increased production of reactive oxygen species has been involved in several chronic diseases, including hypertension. Oxidative stress is, in turn, cause and consequence of this hypertension. The enzyme NADPH oxidase is the major source of reactive species of cardiovascular, renal and neural oxygen. Oxidative stress is associated with endothelial dysfunction, inflammation, hypertrophy, apoptosis, cell migration, fibrosis and angiogenesis; important processes involved in vascular remodeling of hypertension. Despite the large amount of data that involve oxidative stress as a causative factor of experimental hypertension, results in humans are less conclusive. The aim of this review is to describe the role of oxidative stress in the pathophysiology of hypertension. A better understanding of these mechanisms will allow a more comprehensive behavior to this common disease.
Key words: Oxidative stress, Reactive oxygen species, Hypertension

Papel del estrés oxidativo en la patogénesis de la hipertensión arterial

RESUMEN
La producción aumentada de las especies reactivas de oxígeno ha sido implicada con varias enfermedades crónicas, incluida la hipertensión arterial. El estrés oxidativo es, a su vez, causa y consecuencia de esta hipertensión. La mayor fuente de especies reactivas de oxígeno cardiovascular, renal y neural es la enzima NADPH oxidasa. El estrés oxidativo se relaciona con disfunción endotelial, inflamación, hipertrofia, apoptosis, migración celular, fibrosis y angiogénesis; procesos importantes involucrados en la remodelación vascular de la hipertensión arterial. A pesar de la gran cantidad de datos que implican al estrés oxidativo como un factor causante de la hipertensión experimental, los resultados en humanos son menos conclusivos. El objetivo de esta revisión bibliográfica es describir el papel del estrés oxidativo en la fisiopatología de la hipertensión arterial. La mejor comprensión de estos mecanismos permitirá establecer una conducta más integral ante esta frecuente enfermedad.
Palabras clave: Estrés oxidativo, Especies reactivas del oxígeno, Hipertensión arterial

INTRODUCTION

Hypertension (HT) is a chronic disease in which blood pressure (BP) shows le-

vels of 140/90 mmHg or higher. Worldwide, nearly one billion people suffer from HT, and it is estimated that this figure could increase to 1.5 billion by 2025. The exact genesis is unknown, since only about 5 % of hypertensive patients show a precise cause of this condition[1].

At molecular level, numerous factors have been involved in the pathophysiology of HT, for example, the activation of the renin-angiotensin-aldosterone system, inflammation, aberrant G protein-coupled receptor signaling and endothelial dysfunction. Common to these factors is long-term oxidative stress, which causes overproduction of vascular reactive oxygen species (ROS), decrease in nitric oxide bioavailability and a reduction of antioxidant capacity[2]. In the vascular system, the ROS have a physiological role in the control of endothelial function and vascular tone, and an important pathophysiological role in inflammation, hypertrophy, proliferation, apoptosis, migration, fibrosis and angiogenesis. These are important factors in vascular remodeling and endothelial dysfunction associated with HT[3].

Almost all experimental models of HT show some forms of oxidative excess. As the inhibition of ROS-generating enzymes, the antioxidants and ROS scavengers reduce blood pressure, whereas pro-oxidants increase blood pressure, it has been suggested that ROS are causally associated with hypertension, at least in animal models[4]. Although a large amount of data supports the role of oxidative stress in experimental HT, evidence in human HT is weak. A better understanding of these mechanisms will provide a deeper knowledge to ensure better prevention, control and the emergence of new therapeutic targets and novel treatments for this disease.

Oxidative stress (OS) is a state of the cell in which redox homeostasis is altered, that is, there is an imbalance between pro-oxidant and antioxidants[5].

Free radicals are molecules whose atomic structure has an unpaired electron in the outer orbital, which gives them a special configuration of great instability. This makes it very unstable, extremely reactive and short-lived, with a huge capacity for combining nonspecifically in most cases, as well as with the diversity of molecules of the cell structure: carbohydrates, lipids, proteins and nucleic acids[5].

Reactive oxygen species are a variety of free radicals formed from O_2 (**Table**). ROS are inactivated by enzymatic or entrapment mechanisms[5].

HARMFUL EFFECT OF ROS ON BIOMOLECULES

Cellular damage caused by ROS occurs on different biomolecules.

Lipids

This is where the greatest damage occurs, in a process called lipid peroxidation, which affects structures that are rich in polyunsaturated fatty acids, since the permeability of the cell membrane is disrupted, so that edema and cell death follows. Lipid peroxidation or oxidative rancidity is a form of tissue damage which can be triggered by oxygen, singlet oxigen, hydrogen peroxide and hydroxyl radical. Unsaturated fatty acids are essential components of cell membranes, so they are believed to be important for its normal functioning; however, they are vulnerable to the oxidative attack initiated by ROS[6].

The factors that influence the degree of the lipid peroxidation are:

- The qualitative and quantitative nature of the trigger agent.
- The polyunsaturated fatty acids of the membrane and their accessibility.
- Oxygen tension.

Table. Examples of ROS.

O_2^-: Superoxide	$^1O_2$: Singlet oxygen	ROO^-: Peroxyl
OH: Hydroxyl radical	RO^-: Alkoxyl	**ROOH:** Organic hydroperoxide
H_2O_2: Hydrogen peroxide$^{\Omega}$	**HOCl:** Hypochlorous acid	$OONO^-$: Peroxynitrite

$^{\Omega}$ It is not strictly a free radical, but is included as such for its ability to generate OH in the presence of metals (iron, copper). This process is called Fenton reaction.

- The presence of iron.
- The antioxidants in the cell (beta-carotene, alpha-tocopherol, glutathione).
- The activation of enzymes that may terminate the chain reaction, such as glutathione peroxidase.

Once started, the process takes the form of a "cascade" with ROS production leading to the formation of organic peroxides and other products from unsaturated fatty acids. Once formed, these ROS are responsible for the cytotoxic effects[6].

Proteins

There is the oxidation of a group of amino acids such as phenylalanine, tyrosine, histidine, and methionine; there are also peptide chains crosslinks, and finally, there is the formation of carbonyl groups[5].

Deoxyribonucleic acid (DNA)

There are mutations and carcinogenesis, loss of expression or synthesis of a protein due to damage to a specific gene, oxidative modifications of bases, deletions, fragmentation, stable DNA-protein interactions, chromosomal rearrangements and DNA cytosine demethylation that activates genes. The damage may occur due to alterations (inactivation/loss of some tumor suppressor genes that may lead to the initiation and progression of carcinogenesis). The tumor suppressor genes can be modified by a simple change in a critical base of the DNA sequence[5].

VASCULAR GENERATION OF ROS

ROS are produced as intermediates in redox reactions forming H_2O and O_2.

The sequential univalent reduction of O_2 is[7,8]:

$$O_2 \xrightarrow{e^-} O_2^- \xrightarrow{e^-} H_2O_2 \xrightarrow{e^-} OH^- \xrightarrow{e^-} H_2O + O_2$$

In the ROS generated in vascular cells, O_2^- (superoxide anion), and H_2O_2 (hydrogen peroxide) seem to be particularly important. In biological systems, the O_2^- is short-lived due to its rapid reduction to H_2O_2 by the action of superoxide dismutase (SOD), of which three isoforms have been characterized in mammals: copper/zinc SOD (SOD1), mitochondrial SOD (SOD2), and extracellular SOD (SOD3)[9]. The charge on the superoxide anion makes it difficult to cross the cellular membranes, except possibly through ion channels. H_2O_2 has a longer lifespan than O_2^-, is relatively stable and is easily diffusible within and between cells. The distinct chemical properties between O_2^- and H_2O_2 and their different sites of distribution suggest that different species of ROS activate diverse signaling pathways, which lead to divergent, and potentially opposing, biological responses[10].

All vascular cell types produce ROS, including endothelial, smooth muscle, adventitial fibroblasts and perivascular adipocytes, and phagocyte cells (neutrophils, eosinophils, monocytes and macrophages). These ROS may be formed by many enzymes, including xanthine oxidoreductase, uncoupled nitric oxide synthase, mitochondrial respiratory enzymes and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase. Of these, mitochondrial enzymes and NADPH oxidase seem to be particularly important in hypertension[11-14].

PATHOPHYSIOLOGY OF HT ASSOCIATED WITH OXIDATIVE STRESS

Endothelial dysfunction

Endothelial dysfunction has been involved in the pathophysiology of different forms of cardiovascular disease, including HT. This dysfunction can be defined as a deterioration of the actions of the endothelium in vasodilation, increased proinflammatory states and increased prothrombotic activity. These phenomena lead to a state of vascular inflammation that may be partially mediated by the ROS formed by activated mononuclear cells[15].

Vascular OS and HT

The OS is a common mechanism of injury in many types of hypertensive disease processes, and occurs when there is an imbalance between ROS generation and antioxidant defense systems of the body. The ROS family comprises many molecules that have divergent effects on cell function. Indeed, many of these actions are associated with pathological changes observed in cardiovascular disease. ROS effects are mediated by

the redox-sensitive regulation of multiple signaling molecules and second messengers[16-18]. Several studies have shown excessive quantities of ROS in patients with essential HT and in several hypertensive animal models[19-21]; these patients and experimental animals have an inadequate antioxidant state[22], which adds more evidence to the idea that oxidative stress may be involved in essential HT[23]. A strong relationship between BP and some parameters related to OS was recently demonstrated [24]. Other experimental studies showed that mice with genetic defects in ROS generating enzymes show lower values of BP compared to wild mice[25,26]. Furthermore, in cultured vascular smooth muscle cells of arteries from hypertensive rats and humans, ROS production is increased, the redox-dependent signaling is amplified and antioxidant activity is reduced[27]. The beneficial effects of classical antihypertensive agents such as beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers, and calcium-channel blockers are mediated in part by a decrease in vascular OS[28,29].

The sources of ROS in the vascular wall

There is a variety of enzymatic and non-enzymatic sources of ROS in blood vessels. NADPH oxidase is the best characterized. Furthermore, various other enzymes may contribute to the generation of ROS, such as xanthine oxidase, nitric oxide synthase (NOS) and the mitochondrial enzymes.

NADPH Oxidase

It is the primary biochemical source of ROS in the vasculature, particularly the O_2^-. It is also important in the kidney; therefore, it plays an important role in renal dysfunction and vascular damage in pathologic conditions[30]. This system catalyzes the reduction of molecular O_2 by NADPH, which serves as an electron donor in the generation of O_2^-. NADPH oxidase is a positive regulator in HT by humoral and signaling mechanisms. Angiotensin II is the stimulus more commonly studied in the upregulation of NADPH oxidase, but endothelin-1 (ET-1) and urotensin II may also participate in the activation of NADPH oxidase, which leads to an increase in ROS. The best known effect of the O_2^- generated by NADPH oxidase is the inactivation of nitric oxide (NO) in a reaction that forms peroxynitrite, which damages the endothelial vasodilation and uncouples endothelial NOS (eNOS), which leads to additional production of O_2^- [25,31]. In the vasculature, the activation of NADPH oxidase has been strongly associated with HT[32].

Uncoupling of eNOS

The primary function of eNOS is the production of the NO that regulates vasodilatation. However, the deficiency or oxidation of L-arginine and tetrahydrobiopterin (BH_4), which are two essential cofactors in the functioning of eNOS, are associated with the uncoupling of the L-arginine-NO pathway, which results in a decrease in NO formation and an increase in the generation of O_2^-, mediated by the uncoupled eNOS.

The NADPH oxidase is the initial source of ROS. The O_2^- is combined with the NO, formed by eNOS, to form peroxynitrite[33], which in turn oxidizes and destabilizes eNOS to produce additional O_2^- [34]. The O_2^- also leads to the oxidation of BH_4, which promotes eNOS uncoupling and a larger production of ROS.

Xanthine oxidase

Xanthine oxidase is also a major source of ROS in the vascular endothelium[35]. It catalyzes the last two steps of purine metabolism. During this process, the O_2 is reduced to O_2^-. There is evidence that suggests the involvement of this enzyme in HT. Hypertensive rats have shown high levels of endothelial xanthine oxidase and increased production of ROS, which are associated with increased arteriolar tone[30]. In addition to the effects on vasculature, this xanthine may have a role in target organ damage in hypertensive patients[36].

Mitochondria

Mitochondria are the biggest source and target of ROS. Some of the O_2^- that is produced in the intermembrane space may move to the cytoplasm[37]. Ubiquinone or coenzyme Q produces O_2^- when partially reduced (in form of semiquinone), and an antioxidant when it is fully reduced[38]. Complex I produces most of the O_2^- that is generated in mammalian's mitochondria. Complex II and IV are not normally significant sites of ROS production. A moderate uncoupling of complex I is very effective in reducing the production of O_2^- and it has been reported that there is a de-

crease in antioxidant enzyme activity in hypertensive patients[39].

Role of the components of the vascular wall

The endothelium is sensitive to mechanical and hormonal changes; in response, it releases agents that regulate motor function. There is no doubt that the endothelium has a protective and regulatory role through the generation of vasorelaxant substances. Under pathological circumstances, the endothelium produces vasoconstrictors such as ET-1, angiotensin II, urotensin II , superoxide anions, vasoconstrictor prostaglandins and thromboxane A_2, which may be released and contribute to the paradoxical vasoconstrictor effects.

The vascular smooth muscle cells (VSMC) are not only involved in the short-term regulation of blood vessel diameter, and therefore in the regulation of BP, but are also involved in long-term adaptation through structural remodeling. The ROS mediate many of these pathophysiological processes (**Figure**).

The adventitia may contribute to HT either by reducing the bioavailability of NO or by participating in vascular remodeling mediated by ROS.

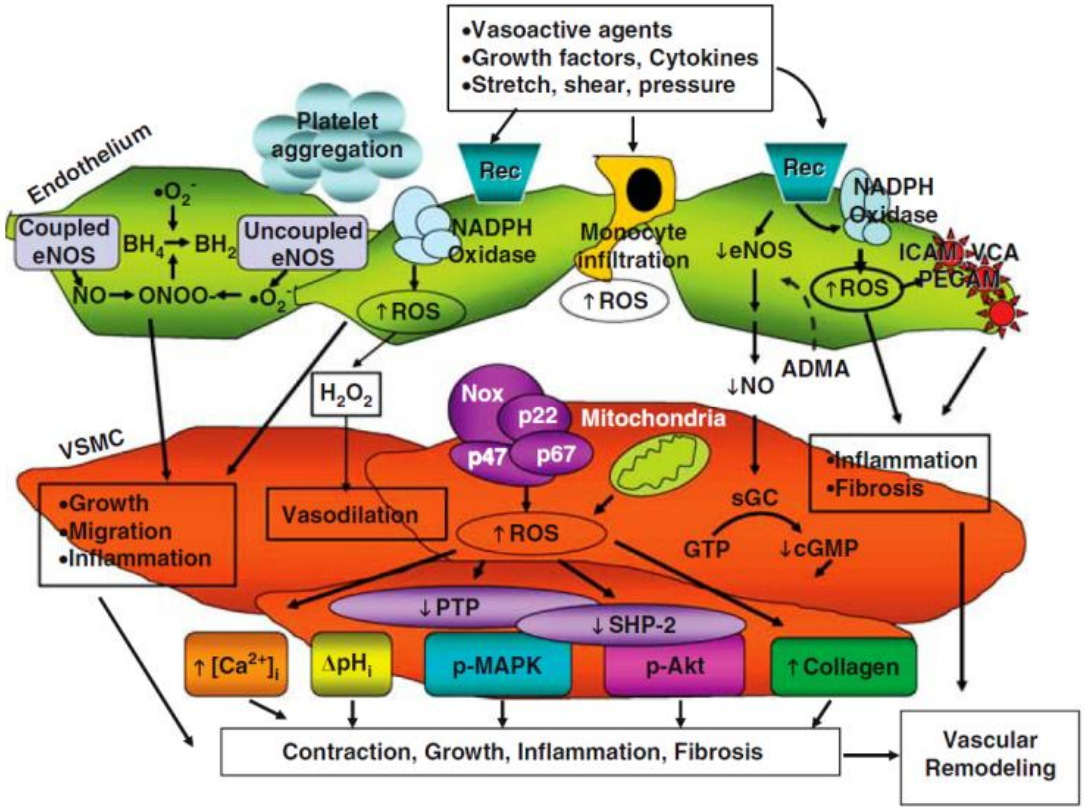

Figura. Vascular remodeling induced by oxidative stress in hypertension. Activation of ROS-generating enzymes, such as NADPH oxidase, simultaneous uncoupling of NOS and mitochondrial enzymes in endothelial and vascular smooth muscle cells results in decreased NO production and increased generation of O_2^- and H_2O_2, which in turn influence redox-sensitive signaling molecules including MAPKs, PTPs, ion channels, transcription factors that induce the expression of pro-inflammatory adhesion molecules such as intercellular adhesion molecules (ICAM), vascular cell adhesion molecules (VCAM), platelet endothelial cell adhesion molecule (PECAM). These processes lead to vascular growth, fibrosis, contraction/dilation, inflammation and platelet aggregation, which underlie vascular damage and structural remodeling in HT and other cardiovascular diseases.

Legend: ADMA (asymmetric dimethylarginine); BH_4 (tetrahydrobiopterin); CGMP (cyclic guanosine monophosphate); GTP (guanosine triphosphate); eNOS (endothelial nitric oxide synthase); MAPK (mitogen-activated protein kinase); NADPH (nicotinamide adenine dinucleotide phosphatase); N(G)-dimethyl-L-arginine (endogenous NOS inhibitor); p- (phosphorylated protein); PTP (protein tyrosine phosphatase); Rec (receptor); sGC (soluble guanylyl cyclase); SHP-2 (SH2 domain-containing protein tyrosine phosphatase-2); VSMC (vascular smooth muscle cells) . Taken from Touyz RM and Briones AM. Hypertension Research. 2011; 5-14[10].

Role of vascular factors and hormones

The NO has an important role as a paracrine regulator of vascular tone. NO, physiologically, inhibits leukocyte adhesion to the endothelium, migration and proliferation of VSMC, and platelet aggregation, thereby maintaining the vascular endothelium healthy. Consequently it has many beneficial effects. A decrease in the bioavailability of NO in the vasculature reduces its vasodilatory capacity and contributes to HT. The enzyme that catalyzes the formation of NO from O_2 and arginine is the NOS, which in fact is a whole family of enzymes. The eNOS is the predominant isoform of the NOS in the vascular wall. The stimulation of the receptors by its agonists leads to the rapid activation of the enzyme and the shear stress and the allosteric modulators are important regulators of its activity[40]. In addition to its vasodilatory and antiproliferative action, NO has an important role that antagonizes the effects of angiotensin II, endothelin and ROS. The NO diffuses as a gas to the underlying smooth muscle where it interacts with different molecular receptors such as soluble guanylyl cyclase.

The normal production of NO has a crucial role in maintaining the physiological conditions within the cardiovascular system. The L-arginine, a substrate for eNOS, appears to be a promising compound for the preservation of NO formation; however, the L-arginine fails to prevent high rates of blood pressure and left ventricular remodeling due to chronic treatment with the methyl ester of N-nitro-L-arginine which is an inhibitor of eNOS[41]. Captopril completely prevents HT by NO deficiency without improving NOS activity. The ON also exerts a negative feedback on ACE. The thiol groups protect NO from oxidation by collecting waste from ROS and forming nitrosothiols, these effects prolong the lifespan and duration of the NO action[42,43].

The reduced levels of NO may be attributed to the increase in ROS. The O_2^- combines with NO to form peroxynitrite which oxidizes BH_4 and destabilizes eNOS to produce more O_2^- [33,34], which further increases the OS. Therefore, the balance between the NO and angiotensin II in the vasomotor center is very important for the regulation of sympathetic tone.

Renin-Angiotensin system

This system has an important role in the development of cardiovascular disease. Angiotensin II is a potent vasoactive peptide that forms in the vascular bed rich in ACE. When its production rises above normal levels, it induces vascular remodeling and endothelial dysfunction, which are associated with high rates of BP; and as it is a potent activator of NADPH oxidase, it contributes to the production of ROS[44,45]. In rats and mice where HT is induced by infusion of angiotensin II, the expression of the subunits of the NADPH oxidase, the oxidizing activity and ROS generation are increased[46]. This angiotensin II not only increases the activity of NADPH oxidase, but also upregulates the activity of SOD, possibly to compensate the increased levels of ROS. In situations where this compensatory effect is effective, the ROS levels may remain normal, even in pro-oxidant conditions. However, when ROS production becomes uncontrollable, the compensatory mechanisms are insufficient and physiopathologic consequences are triggered[47].

Captopril and enalapril prevented the increase in the BP of young rats with induced HT by inhibiting ACE. Captopril, probably due to the antioxidant role of its thiol group, was more effective than enalapril in its antihypertensive effect[48]. However, the NO not only antagonizes the effects of angiotensin II on vascular tone, cell growth and renal sodium excretion, but also down-regulates the synthesis of ACE and the expression angiotensin I receptors. Therefore, the ACE inhibition upregulates the expression of the NOS. The ability of angiotensin II to induce endothelial dysfunction is also due to its ability to downregulate the soluble guanylyl cyclase, causing damage in the signaling of NO/cGMP.

Acetylcholine

In blood vessels, the acetylcholine induces endothelial dilatation by the production of endothelial factors, mainly NO, which diffuses into the layer of underlying vascular smooth muscle and induces vasorelaxation. Decreased bioavailability of NO causes a significant reduction in vasodilation mediated by acetylcholine [48,49] and the result of the overall increase in ROS is a decrease in NO.

ET-1

Endothelins are potent vasoconstrictors isopeptides produced by different vascular tissues, including the vascular endothelium. ET-1 is the main endothelin that is generated in the endothelium and the most im-

portant in the cardiovascular system. When administered in high concentrations, it behaves as a potent vasoconstrictor that is capable of exerting a number of effects, such as altering BP. The ET-1 acts through two receptors, ET_A and ET_B. ET_A receptor mediates vasoconstriction via the activation of NADPH oxidase, xanthine oxidase, lipoxygenase, the uncoupling of eNOS and the enzymes of the mitochondrial respiratory chains. ET_B receptor induces the relaxation of endothelial cells[50]. Many factors that normally stimulate the synthesis of ET-1, (e.g. thrombin and angiotensin II) also increase vasodilators such as prostacyclin (PGI2) and NO, or both, which oppose the vasoconstrictor function of ET-1. Hence it has been reported that essential HT is characterized by increased vasoconstrictor tone mediated by ET-1, in addition to a reduction of ET_B due to the decreased production of NO, or its poor bioavailability.

Urotensin II

Urotensin II is a powerful vasoactive peptide[51], and is, in fact, the most potent vasoconstrictor that has been identified. It works through the activation of NADPH oxidase. The role of urotensin II in HT is still not well understood, because the vasoconstrictor response appears to be variable and highly dependent on the vascular bed; However, vasoconstriction is not the only effect, because urotensin II receptors have been identified in other organs[52,53]. This peptide also seems to function as a potent vasodilator in some isolated vessels[54].

Norepinephrine

The VSMC are primarily innervated by the sympathetic nervous system through the adrenergic receptors. Three types of receptors are present in VSMC: α_1, α_2 and β_2. Norepinephrine stimulates the proliferation of vascular smooth muscle. In addition, the overexpression of NO increases BP due to the activation of the sympathetic nervous system mediated by an increase in OS[16].

Prostaglandins

PGI2 is another vasodilator produced in the endothelium which relaxes the vascular smooth muscle. It is released in higher amounts in response to different compounds such as thrombin, arachidonic acid, histamine and serotonin. The enzyme prostaglandin H2 synthase uses arachidonic acid as substrate to produce prostaglandin H2, which is converted into vasoactive molecules such as PGI2. The isoform of the enzyme prostaglandin H2 synthase-2 may participate in the vascular disorder under conditions of OS; thus, peroxynitrite inhibits the enzymatic activity of PGI2 synthetase and affects the vasodilation mediated by PGI2.

Homocysteine

This molecule may have an important role in the pathogenesis of essential HT. An elevated homocysteinemia decreases the vasodilation of NO, increases OS, stimulates proliferation of the vascular smooth muscle and alters the elastic properties of the vessel wall. Homocysteine therefore contributes to the elevation of blood pressure. In addition, its high levels could cause oxidative damage to the endothelium[55]. Correction of the homocysteinemia by the administration of B_6, B_{12} and folic acid, may be a useful therapy in HT[6]; however, more controlled and randomized trials are needed to establish the efficacy of these therapeutic agents.

KIDNEY AND CENTRAL NERVOUS SYSTEM

So far we have discussed the importance of ROS in blood vessels and their relationship with HT; however, it is also important to emphasize the evidence that hypertensive stimuli, such as high salt intake and angiotensin II, not only promote ROS production at this level, but also in the kidney and the central nervous system. In addition, each of these sites also contributes to HT, or to the adverse effects of this disease[56].

Importance of OS in the kidney

Evidence suggests that ROS play a key role in the pathophysiological processes of various kidney diseases, which are considered causes and consequences of HT. With respect to the glomerular changes, ROS produce glomerulopathic lipoproteins and other glomerular inflammatory lesions[57]. A recent study showed that some lipid conglomerates produce NADPH oxid-

ase activation and the production of ROS, which is an important molecular mechanism that stimulates homocysteine, which favors the oxidative damage to podocytes. This damage may represent an early phenomenon that starts glomerulosclerosis during hyperhomocysteinemia[58]. One of the underlying mechanisms of tubulointerstitial injury, mediated by ROS, is the exposure of tubular cells to LDL, which may cause alterations in the interstitium tubules due to the production of ROS by NADPH oxidase[59]. Angiotensin II not only has a pathogenic role in the progression of tubulointerstitial injury, but also in obstructive nephropathy[60,61]; it also activates NADPH oxidase and generates O_2^- causing hypertrophy of renal tubular cells[62].

There are findings that suggest that a high-fat diet induces renal inflammation and elevation of BP via ROS in the HT of rats[63]. Additionally, the metabolic syndrome is a risk factor for chronic renal failure (CRF), independent of diabetes and HT, probably due to the influence of ROS. The onset and maintenance of renal damage may worsen metabolic syndrome and HT[64].

Various mechanisms of OS are involved in the endothelial dysfunction of CRF[65], where ROS are elevated and are associated with the vascular reactivity of the endothelium and systolic BP[66]. High levels of ROS and asymmetric dimethylarginine have been identified as new risk factors of endothelial dysfunction[67]. Furthermore, high levels of this dimethylarginine have been found in CRF, which are associated with an increase in the thickness of the vascular intima and media, and an increase in cardiovascular accidents[68].

Importance of OS in the central nervous system

Besides the kidneys and blood vessels, the sympathetic nervous system, which is in turn regulated by the central nervous system, is involved in the pathogenesis of HT[69]. Recent studies suggest that increased central sympathetic stimulation increases BP[70]. There is also evidence that increased ROS generation in the brain contributes to the neural mechanisms involved in the HT of rats[71].

The rostral ventrolateral medulla is the largest vasomotor center, and is essential in the maintenance of basal vascular tone[72,73]. Some results show that an increase in the ROS at this level increases the vasomotor stimulation of spontaneous HT in rats and thus contributes to the neural mechanisms of HT through the sympathetic nervous system activation[72]. The paraventricular nucleus of the hypothalamus is, perhaps, the one most strongly associated with the neural mechanisms of the HT associated with ROS[74]. There is evidence that other brain regions are also involved in this type of HT. These studies suggest that the increased production of intracellular O_2^- in the subfornical organ is critical in the development of HT induced by angiotensin II[75].

CONCLUSIONS

Numerous data confirm the importance of ROS in the control of vascular function, by means of the regulation of endothelial function and vascular tone through a strict control of the redox-sensitive signaling pathways. The ROS are mediators in most of the physiological vasoconstrictors that increase the concentration of intracellular calcium. The O_2^- reduces the bioavailability of NO and uncouples the eNOS, which in turn increases even more the concentrations of O_2^-. The uncontrolled production/degradation of ROS causes the OS, which results in cardiovascular, renal and neural damage, and is associated with the elevation of BP. Although oxidative damage is not the only cause of HT, it favors and increases the elevation of BP in the presence of other pro-hypertensive factors. Results from experimental studies, and in animals, indicate the role of OS in the pathogenesis of HT, possibly through the activation of oxidant enzymes, where the NADPH oxidases and the mitochondrial ones have an important role. From a clinical point of view, it is necessary that these data on the causal role of ROS in human HT remain under investigation.

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