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Genetic Polymorphisms Associated with Reactive Oxygen Species and Blood Pressure Regulation

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Abstract

Hypertension is the most prevalent cause of cardiovascular disease and kidney failure but only about 50% of patients achieve adequate blood pressure control, in part, due to inter-individual genetic variations in the response to antihypertensive medication. Significant strides have been made toward the understanding of the role of reactive oxygen species (ROS) in the regulation of the cardiovascular system. However, the role of ROS in human hypertension is still unclear. Polymorphisms of some genes involved in the regulation of ROS production are associated with hypertension, suggesting their potential influence on blood pressure control and response to antihypertensive medication. This review provides an update on the genes associated with the regulation of ROS production in hypertension and discusses the controversies on the use of antioxidants in the treatment of hypertension, including the antioxidant effects of antihypertensive drugs.

Keywords

Hypertension; Oxidative Stress; Reactive Oxygen Species; Pharmacogenomics; antioxidant treatment

Introduction

Hypertension is the most prevalent cause of cardiovascular disease and kidney failure[1], but the prevention and treatment of hypertension are still a challenge[2–4]. According to the 2017 High Blood Pressure Clinical Practice Guidelines, in adults (≥20 years of age), a "doctor's office" reading of 120-129 mm Hg for systolic blood pressure (SBP) even with less than 80 mm Hg for diastolic blood pressure (DBP), is considered as elevated BP[2,3]. An SBP of

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130-139 mm Hg or a DBP of 80-89 is now considered as Stage 1 hypertension, while the previous definition of hypertension ≥140 SBP or ≥90 DBP is now considered as Stage 2 hypertension. In the general population, only about 50% of treated patients achieve adequate blood pressure control[2,4]. The poor efficacy of hypertension treatment and the inter-individual variations in the response to antihypertensive medications have many causes, including non-compliance, but genetic variations could be important contributory factors[4,5].

Reactive oxygen species (ROS) are inevitable by-products of aerobic existence[6]. Disturbance in the normal redox state of cells, either due to the overproduction of ROS or low production of antioxidants, can lead to oxidative stress and specific types of oxygen radicals, such as superoxide anion, H_2O_2 and hydroxyl radical, may damage all components of the cell, including proteins, lipids, and DNA[7,8].

The deleterious effects of ROS and their role in the pathogenesis of hypertension have been extensively demonstrated in experimental models[8–10], but the benefits of antioxidant drug treatment in human hypertension are not clear[8,10–12]. This may be related to the fact that ROS are not always harmful; ROS are able to regulate the activity of cellular signaling pathways such as Ca^{2+} signaling[13,14], and are involved in the regulation of several cells functions such as phenotypic modulation, migration and adhesion, vascular tone, apoptosis and sodium reabsorption between others[13–18]. The oxidative environment in the cell influences gene transcription, post-transcription, translation, and post-translation of proteins. Modifications of the oxidative status may eventually regulate the expression and activity of many proteins such as nuclear factor-kappaB, Nrf2, p38 mitogen-activated protein kinase, NH(2)-terminal Jun kinases/stress-activated protein kinases, hexosamines, and others[13,19–27] evidencing that ROS may be essential for the normal function of cells and biological systems.

Pharmacogenomics aims to individualize therapy based on the individual's genetic profile. There are numerous endogenous oxidants and antioxidant proteins (Figure 1) in different organs, including the kidney, brain, and cardiovascular system, that keep a normal redox balance in the body. Genetic polymorphisms that affect the expression and activity of some of these pro-oxidant or antioxidant genes are associated with human hypertension (Table 1). These polymorphisms could influence the response to antihypertensive drugs, i.e., pharmacogenomics. This review provides an update on the genes associated with the regulation of ROS production in hypertension and discusses the controversies on the use of antioxidants in the treatment of hypertension, including the antioxidant effects of antihypertensive drugs.

1. Mechanisms by which ROS regulate blood pressure

The role of oxidative stress in hypertension has been extensively studied and several mechanisms have been described by which ROS regulate blood pressure (Figure 1).

1.1. Endothelial damage: ROS cause endothelial dysfunction in blood vessels, including renal afferent arterioles and enhance the renal arteriolar vasoconstrictor response to angiotensin II[9,10,12,13,22]. Some of the benefits of superoxide scavengers in hypertension are caused by enhancement of vasodilation and an increase in renal arterial perfusion[23].

1.2. Stiffening of vessels: Recent studies in humans have shown that aortic stiffening precedes the development of hypertension[24]. Mice with smooth muscle overexpression of $p22^{phox}$, a component of NADPH oxidase, develop renal inflammation, fibrosis, and renal dysfunction, prior to the increase in blood pressure, supporting the notion that arterial stiffening induced by oxidative stress and inflammation causes hypertension[25].

1.3 Glomerular damage: Glomerulonephritis without renal insufficiency can be associated with hypertension[26]. ROS can produce glomerular injury by damaging the podocytes, as has been described in Dahl salt-sensitive hypertensive rats[27]. The antioxidant tempol reduces glomerular sclerosis and proteinuria in these animals, supporting a role of ROS in the glomerular injury in Dahl salt-sensitive rats[28].

1.4 Renin-angiotensin system: The development and progression of hypertension due to increased production of ROS have been related to renal vasoconstriction caused by an increase in renal afferent nerve activity and myogenic response and secretion of vasoconstrictor hormones, such as angiotensin II, endothelin-1, and thromboxane[29]. Angiotensin II increases ROS production, inflammation, and renal tubular ion and water transport, and decreases dopamine receptor expression and function, resulting in hypertension[4,5,8,15–17,29–34] . Increasing oxidative stress is one mechanism by which angiotensin II causes renal dysfunction and tissue damage[1,9,10,12,13,22,23,31–38].

1.5 NaCl retention: ROS can regulate ion transport[16–18,23,35–64]. Superoxide, produced by NADPH oxidase, enhances NaCl transport in the renal proximal tubule[16,17,39,44,45,59], thick ascending limb of Henle[41,46,48], and collecting duct[18,47,48]. The voltage-gated proton channel participates in the increased production of superoxide in the renal outer medulla of Dahl salt-sensitive rats[46]. It should be born in mind, however, that ROS can inhibit Na^+/K^+-ATPase and NHE3 activity in the renal proximal tubule[48,50–53].

1.6 Inflammation: ROS activate pro-inflammatory transcription factors, such as NFκB and activator protein-1 and increase the expression of pro-inflammatory proteins[65]. ROS cause the activation, adhesion, and infiltration of inflammatory cells in tissues and organs, including the adipose tissue[8,10,66]. Immune cells, such as macrophages and granulocytes, release ROS to destroy engulfed bacterial or fungal pathogens and this could trigger oxidative stress[67,68]. Vascular stretch is associated with hypertension that could be related to an increase in ROS production and inflammation[8,10,25,69,70].

1.7 Sympathetic nervous system: Renal ROS induce sympathetic activation in renovascular hypertension[71]; chronic antioxidant treatment reduces blood pressure in hypertension characterized by sympathoexcitation and renal oxidative stress[71]. Oxidative stress in the brain, specifically in the cardiovascular regulating center, causes hypertension[72].

2. Genes associated with oxidative stress and blood pressure regulation.

Table 1 lists the genes involved in redox balance that have been associated with hypertension. Table 1 also lists the single nucleotide polymorphisms (SNPs) that are

associated with human hypertension, as well as the genes associated with oxidative stress and hypertension in animal models[73–252].

2.1 Effects of antihypertensive drugs on oxidative stress—Table 2 lists the antioxidant drugs shown to reduce blood pressure in humans and animal models of hypertension[253–328]. These antioxidants have different mechanisms of action and various combinations may have synergistic effects on the regulation of blood pressure. For example, the antihypertensive effect of the combination of zinc sulfate, ascorbic acid, α-tocopherol, and β-carotene may be due to an increase in the bioavailability of NO[324]. By contrast, antioxidant drugs such as vitamin E, under certain conditions, can also increase the blood pressure in mice[325]. Vitamin E at doses greater than 150 IU daily increases the risk of all-cause mortality in humans[326]. The combination of vitamin C and polyphenols has also been reported to increase blood pressure variability[229], and the antioxidant properties observed *in vitro* may not be observed *in vivo*[328]. The effect of chemicals on ROS production and blood pressure is complex and not easily predictable.

2.2 Pharmacogenomics of antioxidant drugs—Increased ROS production is involved in the pathogenesis of many [1,5,8–17,22,23,25,28–44,48,57,60,62–64,68,71,72,86,89,92,104,138,140–154,162,163,173,189,197,210,214,218,219,221–233,236–244,246–25], but not all cases[232–234] of hypertension. Deletion of the gene that encodes thioredoxin reductase 2 increases ROS production but blood pressure is actually decreased[235]. Nevertheless, genetic polymorphisms in pro-oxidant or antioxidant genes may affect the redox balance in the kidney, cardiovascular system, and brain (Figure 1), among others. Therefore, genetic polymorphisms may be involved in the inter-individual variability of the effects of antihypertensive medications. Many genes involved in ROS production and their polymorphisms associated with hypertension have been identified (Table 1).

2.2.1 Polymorphisms in Pro-oxidant Genes: Angiotensinogen (AGT) is converted to angiotensin I by renin and angiotensin 1 to angiotensin II by angiotensin converting enzyme (ACE); angiotensin II induces oxidative stress by stimulation of NADPH oxidase activity[15,22,23,29–31,36,37,42,47,48,56,57]. Polymorphisms in *AGT* are associated with hypertension in humans[78–83]; a haplotype of human *AGT* gene containing −217A or −6G increases blood pressure in transgenic mice[76,77].

The NADPH oxidase (NOX) family has seven members which are classified into three groups: group 1 is comprised of *NOX1*, *NOX2, NOX3, NOX4*; group 2 has *NOX5* as the only member, and group 3 is comprised of *DOUX1* and *DOUX2*[48,332]. Increased NOX activity is implicated in many disease states, including hypertension and renal disease[5,10,15,23,25,29–32,36,47,48,56,57,125–147,332–344].

p22^{phox} (*CYBA*, cytochrome B-245 alpha chain) is a membrane-associated protein that plays a crucial role in the activation of *NOX1, NOX2, NOX4*[48], and *NOX5*[333]. Mutations of *CYBA* lead to autosomal recessive forms of chronic granulomatous disease[334]. Germline deletion of *CYBA* in mice[335] or silencing of *CYBA* in Sprague-Dawley rats does not affect basal blood pressure but ameliorates angiotensin II-induced hypertension[125,126]. However,

smooth muscle-specific overexpression of $p22^{phox}$ in mice increases blood pressure that is normalized in the offspring of dams crossed with *Rag1*$^{-/-}$ mice[25]. Polymorphisms in the *CYBA* promoter in the spontaneously hypertensive rat (SHR) increase the gene expression of *CYBA*[336]. Several polymorphisms of *CYBA* that could affect the production of ROS have also been reported in humans[334]. Some other *CYBA* gene variants are associated with decreased NOX2-dependent ROS generation but their association with blood pressure has not been studied[128]. Other *CYBA* gene variants are associated with increased ROS production and hypertension in several ethnic groups[129,130,131,134–136,337]. However, although *CYBA* 242C>T is associated with endothelial dysfunction, it is not associated with hypertension in an Asian-Indian population[338]. A meta-analysis found no association of *CYBA* 242C>T with hypertension[134]. *CYBA* 242C>T may be protective of coronary artery disease in an Asian population[132] but increases the risk of diabetes mellitus[133]. In an Asian-Indian population, the haplotypes rs8854A/rs9932581G/rs4873C and rs8854G/rs9932581G/rs4873C are positively associated with increased blood pressure and oxidative stress while the haplotype rs8854G/rs9932581A/rs4873T is inversely correlated with blood pressure and oxidative stress[339].

NOX5 gene, which is present in humans but not rodents, is expressed to a greater degree than the other isoforms in renal proximal tubule cells from hypertensive humans[340]. Certain *NOX5* SNPs have been reported to be associated with decreased (*NOX5* 77M>K) activity and ROS production[341]. However, mice with podocyte-specific human *NOX5* expression develop renal disease and high blood pressure[342]. Genes that interact with NOXs have polymorphisms that may also be associated with increased ROS production and hypertension. For example, a polymorphism in the 3'UTR (rs11169571 [T>C] of the activating transcription factor 1 *[ATF]*) may be involved in essential hypertension by induction of *NOX1* and increase in ROS production[343].

The minor T allele of rs6967221 in *RAC1*, one of the cytosolic components of *NOX1, NOX2*, and *NOX3*, is associated with a decreased systolic blood pressure response to high sodium intake[152].

Endothelin-1 (ET-1) is a potent vasoconstrictor which can increase ROS production by stimulation of NADPH oxidase activity[344]. A polymorphism of type A endothelin-1 receptor (rs5335, 70C>G) is associated with increased night-time blood pressure[105]. Polymorphism at rs9349379 in *PHACTR1*, a distal regulator of EDN1, is associated with a lower risk of hypertension[345].

Myeloperoxidase (MPO) produces hypochlorous acid (HOCl) and chloride anion (Cl^-) (or equivalent) from H_2O_2 during the neutrophil's respiratory burst. MPO released during chronic inflammation produces tissue damage and high MPO levels may exacerbate diseases associated with atherosclerosis. However, MPO-deficient mice unexpectedly have increased atherosclerosis, relative to their wild-type littermates[346], indicating that the role of MPO in cardiovascular disease is still unclear or that this murine model may not reflect human disease. The −463G>A polymorphism located in the promoter region of the *MPO* gene has been associated with hypertensive nephrosclerosis in patients on dialysis[120] and hypertension with or without carotid atherosclerosis in Chinese[121,122]. However, this

polymorphism has been associated with a decreased risk of hypertension in Russian females[123].

Xanthine dehydrogenase (XDH), aka xanthine oxidoreductase (XOR) and xanthine oxidase (XO) are interconvertible single gene products. XDH is the primary form but is converted to XO irreversibly by proteolysis or reversibly by oxidation of Cys residues. XO catalyzes hypoxanthine or xanthine to form hydrogen peroxide and uric acid while XDH produces NADH[347]. In the blood, XDH exists mainly as XO[242]. *XOD* is extensively expressed in body organs, such as the liver, muscle, brain, and kidney[348]. XDH-mediated increase in ROS has been described in salt-sensitive hypertension and glucocorticoid induced hypertension[242]. In a Spanish cohort, −337G>A and 565+64T>C and their haplotypes were found to be associated with higher systolic and diastolic blood pressures and malondialdehyde[242]. The variation in uric acid production, as related to polymorphisms of *XDH*, increases the risk of hypertension[240].

Lipoxygenases catalyze the dioxygenation of polyunsaturated fatty acids to their corresponding hydroperoxy derivatives. Arachidonate 15-lipoxygenase (*ALOX15*) gene rs2664593 has been reported to be associated with air pollution and increased left ventricular mass[349]. A nonsynonymous polymorphism in *ALOX12*, 261R>Q, has been reported to be associated with essential hypertension and urinary levels of 12-hydroxyeicosatetraenoic acid (12(S)-HETE)[350]. Mice lacking macrophage 12/15 lipoxygenase are resistant to L-NAME and DOCA-salt hypertension[351].

Cyclooxygenase-2 (COX2, *PTGS2*) can produce ROS, which can increase cyclooxygenase expression and activity[92]. −765GC+CC genotypes of *PTGS2* are inconsistently associated with chronic obstructive pulmonary disease that could be related to increased ROS production[90,91]. *PTGS2* SNPs have been associated with increased high blood pressure in humans[352]. Germline deletion of *Cox-2* in mice increases blood pressure[353].

The mitochondrion, which is one of the most important sources of ROS, has been extensively associated with oxidative stress and hypertension[8,12,13,145,228]. ROS-induced hypertension could involve the mitochondria in the brain[72] and in the kidney[354,355,356]. Cytochrome P450 genes are important sources of ROS in the mitochondria, endoplasmic reticulum, and plasma membrane. P450 proteins are a family of hemoproteins that catalyze the oxygenation of a wide variety of compounds and, in general, is the terminal oxidase enzyme in the electron transfer chain in the mitochondria[95]. The efficiency of electron transfer depends on many conditions. For example, SNPs in the gene encoding Cytochrome P450 affect the regulation of ROS production and the redox balance[357,358]. SNPs in the cytochrome P450 gene family have also been associated with high blood pressure in several different populations [96,98,360,361] but protective in a North Americans [97]. CYP-epoxygenase decreases renal sodium transport, in part, by inhibition of ENaC activity in the cortical collecting duct[362]. *CYP17A1* (rs11191548) is associated with increased left ventricular mass in patients with hypertension and preserved left ventricular ejection fraction[363].

2.2.2 Polymorphisms of antioxidant genes: Oxidative stress can occur not only from an increase in pro-oxidant activity but also from impaired antioxidant activity. SNPs of genes

that decrease antioxidant gene function/expression could induce oxidative stress and increase blood pressure. Our group and others have provided evidence for the importance of the antioxidant properties of dopamine receptors in the kidney in the regulation of renal sodium transport and blood pressure, as well as dopamine receptor-mediated non-renal mechanisms in the regulation of blood pressure[5,16,32,38–40,62,64,165,170,173,174,178–188,364–367]. Germline deletion of the *DRD2* results in oxidative stress dependent-hypertension[252]. DJ-1 (*Park7*) and paraoxonase 2 (PON2)[146,163] are involved in the antioxidant properties of the D_2R in the kidney. Polymorphisms associated with deficiency of *DRD2* expression are associated with essential hypertension in different populations[171,172,174]. *PON1* SNPs (e.g., −108C>T, 192Q>R) are risk factors for endothelial dysfunction and hypertension[212,213]. Genetic depletion of *DJ-1*, a mitochondrial antioxidant[368], results in renal oxidative stress and high blood pressure in mice[163]. Dysfunction of mitochondrial proteins that decrease ROS production (e.g., *SOD2*, *UCP2* [*vide infra*]) may be involved in the target-organ damage associated with hypertension[369].

Polymorphisms in uncoupling protein 2 (*UCP2*), a mitochondrial gene with antioxidant properties, are associated with an increased risk for diabetic kidney disease[370]. In addition, a common human polymorphism of the *UCP2* gene, −866 G>A, has been associated in hypertension[239].

Glutathione (GSH) is another antioxidant enzyme that plays a role in blood pressure regulation[371]. Glutathione *S*-transferases (GSTs) catalyze the conjugation of the reduced form of GSH. The GST superfamily constitutes up to 10% of the cytosolic protein in some mammalian organs[372]. Low blood level of GST-π concentration is predictive of the time of the onset of stroke[373]. The *GSTA1*B* allele is considered as a genetic risk factor for hypertension in Japanese[374]. The association between the *GSTT1* null and hypertension was reported in Italian women but not men[198] and *GSTM1* null genotype with hypertension in Korean men and women[199]. The *GST* P1b-1b genotype causes prolonged exposure to ROS and increased risk of pre-eclampsia[375]; *GSTP1* 313A>G with preeclampsia in Maya-Mestizo women[201]. However, a meta-analysis showed no association of *GSTM1* and *GSTT1* polymorphisms and the risk of hypertension[376].

Glutathione peroxidases (GPXs) are important in the reduction of lipid hydroperoxides and H_2O_2 to water; *GPX4* rs713041 (718T>C) may be a predictor of cerebral stroke in hypertensive Russians[196]. *GPX3* s3828599 (T>C) is associated with hypertension in Han Chinese[195].

Heme oxygenase catalyzes the degradation of heme, resulting in the formation of iron, carbon monoxide, and biliverdin, which is subsequently converted to bilirubin by biliverdin reductase[188]. *HO-1* short repeats (<25) are associated with lower risk of cardiovascular disease; *HO-1* short repeats are associated with increased *HO-1* activity[206].

Extracellular superoxide dismutase (EC-SOD, aka SOD3, Cu-Zn SOD) protects the tissues from oxidative stress by converting the toxic superoxide anion into less toxic hydrogen peroxide (H_2O_2)[8–10,12,13,222,224,231–233,377]. The T-A or T-A-C haplotype, rs13306703 and

rs2536512 with or without 17998895 in *SOD3* gene increases the risk for essential hypertension in a Japanese population[190]. By contrast, 172G>A (rs2536512) polymorphism, by itself, is associated with a decreased risk for hypertension in Spaniards[230] but is not associated with hypertension in other populations[233]. Germline global deletion of *SOD3* in mice causes oxidative stress and hypertension[189]. However, an earlier and later study by others did not find *SOD3* knockout mice to be hypertensive but found them to have increased hypertensinogenic response to NO inhibition or angiotensin II infusion[231,232].

Catalase (CAT) catalyzes the conversion of H_2O_2 to water and oxygen. SNPs in the *CAT* gene promoter region, *CAT*-844 AA and *CAT*-262 CT or TT, have been associated with essential hypertension among Chinese[157], smoking Russians[154], Greeks[155], but not African-Americans and Caucasians[156]. However, *CAT* haplotype [−844G,−89A,−20T] relative to the *CAT* haplotype [−844A,−89T,−20C] was predictive of a decrease in diastolic blood pressure after bariatric surgery in a French population[378]. In individuals with low-level lead exposure, *CAT* rs769217, C>T, is associated with increased blood markers of oxidative stress and hypertension[379]. By contrast, *CAT* rs1049982, −20 C>T, is associated with lower blood pressure[230]. In individuals with a family history of hypertension, 20-35% of the variation of plasma hydrogen peroxide may be due to genetic factors[380, 381].

The transcriptional coactivator peroxisome proliferator-activated receptor-gamma coactivator 1 alpha (PGC-1 α) is an important regulator of energy control[382] and is a master regulator of manganese *SOD2* and *UCP-2*, both of which are mitochondrial proteins with antioxidant properties[383]. Polymorphisms in *PGC-1α* gene have been associated with hypertension in several studies, in males with Gly482Ser+A1704G haplotype, but the 482SS is protective of hypertension in Caucasian males in two studies and females in one study[215–217].

These aforementioned studies show that SNPs of genes involved in redox balance are involved in blood pressure regulation.

3. Treatment of oxidative stress in humans with hypertension

Despite the numerous studies demonstrating a role of oxidative stress in cardiovascular diseases and the beneficial effects of antioxidants in the treatment of hypertension in animal models (Table 2), it has been difficult to demonstrate a role of oxidative stress in the pathogenesis and treatment of hypertension in humans[305,384]. Indeed, oxidative stress may be the consequence and not the cause of hypertension in humans[385].

Several antioxidant drugs, such as vitamin C, vitamin D, vitamin E, and bardoxolone alone or in combination[302–307,310–312,314–317,319,320,324,384,386] with other antioxidants have been shown to prevent the deleterious effects of oxidative stress or hypoxia in different cardiovascular and renal diseases, including hypertension but some with undesirable side effects[308,309,318,325,326,327,387,388]. A meta-analysis in 135,967 participants in 19 clinical trials showed that high doses of vitamin E increased mortality[387]. The authors of a more recent meta-analysis concluded that supplements with vitamin E decreased cardiovascular mortality risk and folic acid decreased the risk for cardiovascular disease, while β-carotene, eicosapentanoic acid, magnesium, selenium, vitamins D and K, and zinc did not show

significant risk reduction of cause-specific death or cardiovascular disease[388]. Thiosulfate, a hydrogen sulfide donor, which can decrease oxidative stress, has been reported to improve vascular endothelial function in hypertensive humans[389,390]. Bardoxolone, a Nrf2 agonist that increases the expression of several antioxidants, was initially shown to improve renal function in humans with advanced chronic kidney disease and type 2 diabetes[391,]. However, it was withdrawn from further clinical trials because of serious adverse events, including heart failure and cardiovascular events, and mortality[392,393].

Antioxidant treatment with ascorbic acid was initially shown to lower blood pressure in a limited number of patients with hypertension[394,395]. However, larger studies have not found a clear beneficial effect of antioxidant vitamins on the development or control of blood pressure[396,397]. The combination of ascorbic acid and polyphenols actually resulted in a higher blood pressure variation[327]. Therefore, there is insufficient evidence to support the use of dietary supplements in the primary prevention of cardiovascular diseases[388]. However, the period of treatment and doses[398] could be crucial in the beneficial or deleterious effects of antioxidant therapy. What is evident from these published data is that the effect of the ROS on the cardiovascular system is more complex than expected and innovative approaches must be formulated to resolve these discrepant results.

3.1 Antioxidant effect of antihypertensive drugs—The ability of some angiotensin II type 1 receptor blockers[305,399] and ACE inhibitors[305,400] to reduce ROS production and oxidative stress is well known. The classical renin-angiotensin system increases ROS production[22,23,31,34–37,56,57,64] and thus, the beneficial effects of some of the antihypertensive drugs may be due to their ability to inhibit NADPH activity. The sulfhydrylated ACE inhibitors (e.g., captopril, epicaptopril, and S-zofenopril but not enalaprilat, perindoprilat, or quinaprilat[401,402]) contain a thiol radical that *per se* has antioxidant properties and may prefer to scavenge general radicals rather than superoxide radicals[400,401]. Although, the antioxidant effect of sulfhydrylated ACE inhibitors has been ascribed to the thiol group, the vasodilatory effect of S-zofenopril may be due to hydrogen sulfide[403]. The antioxidant effects of other antihypertensive drugs, such as β adrenoceptor blockers[305,404,405] and calcium channel blockers[305,406] have been reported, as well. Hypertension and oxidative stress associated with chronic ethanol intake can be prevented by the β-adrenoceptor blocker, nebivolol[407,] Therefore, part of the beneficial effects of some antihypertensive drugs may due to their ability to decrease ROS production. However, a novel angiotensin II type 1 receptor blocker has been reported to induce oxidative stress in a hepatocellular cell line HepG2[408].

These disparate effects of anti-hypertensive drugs on ROS production and blood pressure regulation may be related to the fact that, as aforementioned, ROS have beneficial effects on cell function[10,13–21]. Anti-oxidants at high concentrations may have pro-oxidant effects[409] and the excessive antioxidation could have deleterious consequences. For example, a small but continuous production of ROS expression during physical exercise enhances antioxidant defenses and induces the expression of antioxidant enzymes; vitamin C supplementation decreases the endurance capacity in humans and rats[410] and diminishes some of the increased skeletal muscle adaptations following acute exercise[411]. While physiological doses of anti-oxidants may be beneficial, excessive antioxidation could have deleterious

consequences because the “remodeling” of skeletal muscles with exercise is dependent on reactive oxygen and nitrogen signaling[412]. The duration of the antioxidant effects may also be transient. For example, the biomarkers of oxidative DNA damage were attenuated by daily consumption of blueberries for 4 weeks in pre- and stage 1-hypertensive postmenopausal women, however, these effects were not found after 8 weeks[413].

Increased production of mitochondrial ROS plays a role in the pathogenesis of diabetic nephropathy[414] and hypertension[355]. However, ROS produced by *NOX4* can induce endothelial angiogenesis and protect against chronic cardiac overload[415]. Moreover, diabetic complications are associated with a decrease in mitochondrial ROS production but may help in the preservation of renal glomerular function during hyperglycemia [416,417]. Therefore, “normal” physiological levels of mitochondrial superoxide are important for healthy mitochondrial function[418].

The amount of ROS formed, type of ROS formed, i.e., superoxide *versus* H_2O_2, source, duration, and their subcellular locations may be determinants on the consequences of ROS production on cell function. It is universally accepted that a redox imbalance induced by an excessive and uncontrolled ROS production could have deleterious consequences on blood pressure regulation. However, the excessive intake or expression of antioxidants could also have delirious consequences on the cardiovascular system.

4. Conclusion

Several genetic polymorphisms that affect pro-oxidant and antioxidant systems, directly or indirectly, are associated with hypertension. Antioxidants can reduce the blood pressure in humans and animal models of hypertension. Antihypertensive drugs can also have anti-oxidant effects. However, an indiscriminate decrease in ROS production can have deleterious consequences. ROS are involved in the regulation of essential cellular processes. Thus, the long-term administration of drugs with antioxidant properties may impair vital cellular function, resulting in undesirable side effects. Studies are needed to elucidate the role of pharmacogenomics in redox balance in the treatment of hypertension.

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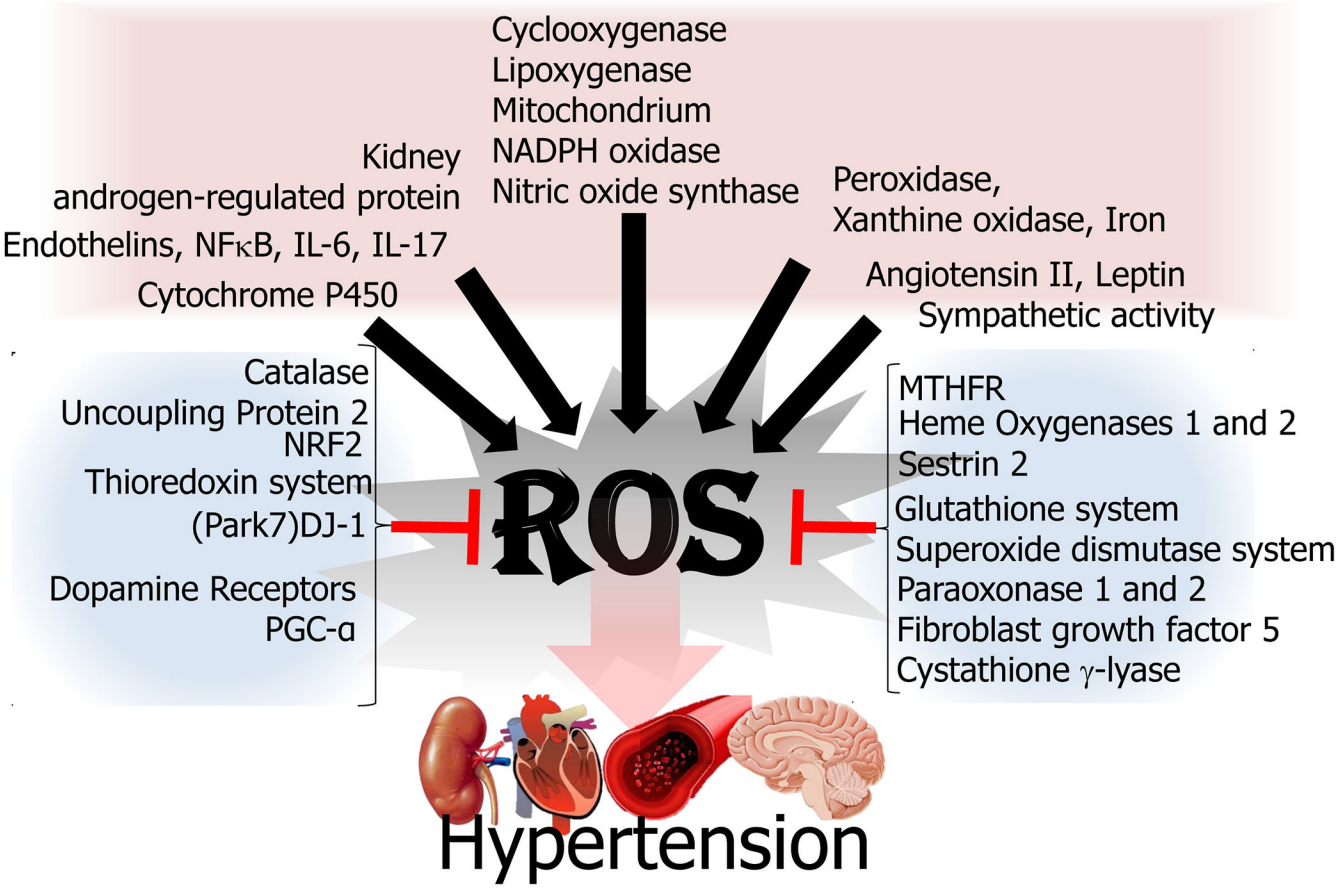

Abbreviations: MTHFR:Methylenetetrahydrofolate reductase; NRF2: Nuclear factor (erythroid-derived 2)-like 2, also known as NFE2L2; PGC-α: Peroxisome Proliferator-activated receptor γ coactivator 1-α (PGC-α); MPO: Myeloperoxidase ; IL: Interleukin.

Figure 1. Genes associated with redox balance regulation and Hypertension.

The presence of the SNPs in pro-oxidant and antioxidant genes could increase the ROS production in the brain, cardiovascular system, heart, and kidney to induce hypertension.

Table 1.

Genes associated with hypertension and oxidative stress in humans and/or animal models of hypertension.

Genes associated with oxidative stress	Associated with hypertension in animal models	SNPs	Associated with hypertension in humans
Polymorphisms of pro-oxidant genes			
Activating transcription factor 1 (*ATF1*)		rs11169571	[73]
Aminopeptidase A (*APA*)		Aminopeptidase-A (stop), rs2290105	[84, 85]
Angiotensinogen (*AGT*)	[37,76,77]	−6G>A, −20A>C, −152A>G, −217G>A, rs5050 M235T (rs699)	[78–83]
Angiotensin II type 1 receptor (*AGTR1*)	[86, 87]	rs5186 (1166A>C)	[84]
Arachidonate 15-lipoxygenase (ALOX1){351]		261R>Q	[350]
Cycloxygenase-2 (*COX2, PTGS2*)		−765G>C, rs2143417	[88–90]
Cytochrome P450	[91–94]	*CYP2*C8*3, *CYP 450* 2J2(−50G>T), *CYP3*A5*3 (rs776746) (Japanese), *CYP3*Ar5*1 (European- and African-Americans), *CYP4*A11 (rs1126742), *CYP*17A (rs11191548)	[91,96–103,200,356–358]
DNA-Binding Factor *NFkB*	[104]		
Endothelin I		rs5335 (70C>G), rs5370 (198G>T)	[105,359]
Hemojuvelin (*HJV*)		rs16827043, rs7536827	[106]
Interleukin-6 (*IL-6*)	[107]	rs1800795 (−174G>C), rs1800796 (−572C>G)	[108–111]
Interleukin-17A (*IL-17A*)	[112]	rs2275913 (G>A)	[113]
Iron regulatory protein (*HFE*)		rs1799945 (63H>D)	[114]
Leptin (*LEP*)	[115,116]	II/I tetra nucleotide repeat, rs799039(G2548A)	[117,118]
Leptin receptor (*LEPR*)		rs1137101 (223Q>R), rs1137100 (109K>R)	[117–119]
Myeloperoxidase (*MPO*)		rs2333227(−463G>A)	[120–124]
NADPH oxidase p22phox (*CYBA*)	[25,125,126]	rs9932581 (930A>G), rs78935588 (640A>G) rs7195830 (49A>G), −675A>T rs4673 (242C>T), rs8854A, rs9932581G	[127–139]
NADPH oxidase 1 (*NOX1*)	[140, 141]		
NADPH oxidase 2 (*NOX2*)	[142–145]		
NADPH oxidase 4 (*NOX4*)	[147]		

Genes associated with oxidative stress	Associated with hypertension in animal models	SNPs	Associated with hypertension in humans
Neutrophil cytosol factor 2 (*NCF2*)		rs12094228, rs16861188, and rs12066019	[148]
Nitric oxide synthase 3 (*NOS3*)	[149]	894G>T (rs1799983)	[150,151]
RAC1		rs6967221	[152]
Xanthine dehydrogenase/oxidase (*XDH*)		rs11904439, rs148756340	[240]
Polymorphisms of antioxidant genes			
Catalase (*CAT*)	[153]	rs769214 (−844G>A), rs1001179 (−262C>T), −20C>T, rs769217	[154,155,157] [230,279]
Cystathione γ-lyase (*CSE*)	[158–160]	rs482843	[161]
DJ-1 (PARK7)	[162,163]		[164]
Dopamine 1 receptor (*DRD1*)	[32,165]	(−48A>G, −94G>A rs1799914, rs4867798)	[166–170]
Dopamine 2 receptor (*DRD2*)	[32,252]	rs6276, rs6277, rs1800497	[171–176]
Dopamine 3 receptor (*DRD3*)	[178–180]	rs9880168	[169]
Dopamine 4 receptor (*DRD4*)		−521C>T, DRD4 long allele	[182–184]
Dopamine 5 receptor (*DRD5*)	[185–188]	No associations published	
Fibroblast growth factor 5 (*FGF5*)		rs16998073	[192,193,200]
Glutathione	[197]		
Glutathione peroxidase (*GPX1, GPX3, GPX4*)	[194]	rs713041 (718C>T) rs3828599	[195,196]
Glutathione S-transferase Alpha 1 (*GSTA1*)		GSTA1*B allele GSTA1*B allele +GSTM1 null	[374]
Glutathione S-transferase Mu 1 (*GSTM1*)		GSTM1 null GSTM1 + GSTT1 null	[198,199,202] [374]
Glutathione S-transferase Mu 3 (*GSTM3*)		−63A>C	[203]
Glutathione S-transferase Pi 1 (*GSTP1*)		A313	[201]
Glutathione S-transferase Theta 1 (*GSTT1*)		GSTT1 null	[198]
Heme oxygenase-1 (*HO-1*)	[204,205]	<27 GT repeats rs9607267	[206]
Heme oxygenase-2 (*HO-2*)	[207]		
Kidney androgen-regulated protein (*KAP*)	[208–210]		

Genes associated with oxidative stress	Associated with hypertension in animal models	SNPs	Associated with hypertension in humans
Methylenetetrahydrofolate reductase (*MTHFR*)		677C>T	[201,211]
Nuclear factor (erythroid-derived 2)-like 2, also known as NFE2L2 (*NRF2*)	[163]		
Paraoxonase 1 (*PON1*)		192Q>R, −108C>T	[212,213]
Paraoxonase 2 (*PON2*)	[146]		
Peroxisome proliferator-activated receptor γ coactivator 1-α (*PGC-α*)	[214]	482G>S, 482G>S+1704A>G haplotype	[215–217]
Sestrin 2 (*SESN2*)	[218]		
Superoxide dismutase 1 (*Cu-Zn SOD*)	[220–226]		
Superoxide dismutase 2 (*Mn SOD*)	[219,227,228]		[150]
Superoxide dismutase 3 (*EC SOD*)	[189,231,232]	rs13306703 + rs2536512 +/− rs1799895	[190,230]
Thioredoxin (*TXN*)		rs2301241 (−793T>C)	[230]
Thioredoxin interacting protein (*TXNIP*)	[234]		
Thioredoxin reductase (*TXNRD2*)	[235]		
Uncoupling protein 2 (*UCP2*)	[236–238]	−866 G/A	[239]

Table 2.

Antioxidant drugs that decrease blood pressure in humans with hypertension and animal models of hypertension.

Antioxidant	Species	Mechanism of action	References
N-acetyl cysteine	human, mouse, rat	Direct antioxidant, precursor of cysteine reduced glutathione, breaks disulphides	[243–247]
Apocynin	mouse, rat	Prevents NADPH oxidase assembly	[248–252]
Allicin/Aliin/S-allylcysteine (garlic)	human	Reduces 8-hydroxy-2'deoxyguanosine, malondialdehyde, angiotensin II-generated ROS	[253–256]
L-arginine	human, mouse, rat	Substrate for NO production	[257–259]
Bardoxolone	human, mouse, rat	Nrf2 inducer	[260,261]
L-carnitine	human, mouse, rat	Key compound in the transport of long-chain fatty acids into mitochondria for β-oxidation	[262,264–266]
Catechins			
Black tea (theaflavin-polyphenol)	rat	Stimulates NO and H2S production, Decreases endothelin-1 and angiotensin II	[267]
Green tea (polyphenols)	human	Antioxidant, inhibits catechol-O-methyl transferase, NO release	[267–269]
Coenzyme Q10	human, mouse, rat	Reduces mitochondrial superoxide production by increasing the efficiency of electron transfer from Complexes I and II down the mitochondrial electron transport chain	[270–273]
Curcurmin	human, mouse, rat	A herbal supplement used as a food additive with antioxidant properties at low concentrations, induces HO-1	[274–277]
Hemin	mouse, rat	HO-1 inducer (can induce mitochondrial dysfunction)	[278–280]
Hesperidin	human, rat	Free radical scavenger and enhancer of antioxidant pathways via ERK/Nrf2, inhibits RAS	[281–283]
α-Lipoic acid	human, mouse, rat	Free radical scavenger and activator of anti-oxidant recycling	[284–286]
Melatonin	human, rat	Free radical scavenger and up-regulator of antioxidant enzymes.	[287–290]
Quercetin	human, mouse, rat	Free radical scavenger	[291–294, 419, 420]
Resveratrol	human, mouse, rat	Activator of sirtuins and PGC-1α, involved in stress response, and Nrf2	[295, 296, 421]
Tempol	human, mouse, rat	Redox-cycling nitroxide and SOD mimetic	[9,16,28,29,34,297,422]
Troxerutin	mouse, rat	Flavonoid (hydroxyethylrutoside) with antioxidant properties	[298,299]
Vitamin C	human, mouse, rat	Free radical scavenger	[11,300–306]
Vitamin D	human, mouse, rat	Inhibits iron-dependent liposomal lipid peroxidation	[10,307–319]

Antioxidant	Species	Mechanism of action	References
Vitamin E	human, mouse, rat	Free radical scavenger, impairs ROS signaling	11,303,320–323]