Published in final edited form as:

J Am Soc Hypertens. 2014 August ; 8(8): 601–603. doi:10.1016/j.jash.2014.07.002.

Oxidative Stress

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Oxidative stress is a condition in which the production of reactive oxygen species (ROS) exceeds the antioxidant capacity of the cell or organism. A variety of enzymatic sources produce ROS in mammalian cells, including the NADPH oxidase, the mitochondria, xanthine oxidase and in some circumstances, the nitric oxide synthases. In several pathophysiological states, including atherosclerosis, diabetes, obesity, lung disease, aging and hypertension, ROS production by one or more of these enzymes is increased. In addition, mammalian cells possess a variety of antioxidant defenses, including the superoxide dismutases, catalase, the glutathione peroxidases, thioredoxins, peroxiredoxins and small molecules such as glutathione and uric acid. A reduction of these endogenous antioxidants can also promote oxidative stress. Changes in the balance between ROS and antioxidant scavenging can be localized to subcellular components, such as the mitochondria, the nucleus or other organelles. In this case, measures of the global balance between ROS production and scavenging in a cell, a tissue or an intact animal or human might not reflect perturbations within these small subcellular compartments. As discussed later in this chapter, this has also emphasized the need to develop therapies that can be directed toward subcellular components.

There has been enormous interest in the role of oxidative stress in the pathogenesis of hypertension for the past two decades. Treatment with membrane-targeted forms of superoxide dismutase and superoxide dismutase mimetics lowers blood pressure in various experimental models of hypertension, including the spontaneously hypertensive rat and angiotensin II-induced hypertension. In the 1990s, it was discovered that a major signaling mechanism of angiotensin II is to activate the NADPH oxidase, which is a major source of ROS in many mammalian cells. Mice lacking components of the NADPH oxidase are protected against both angiotensin II and DOCA-salt induced hypertension. There are several different NADPH oxidase catalytic subunits, termed Nox proteins, which have different modes of activation, tissue distributions and levels of activity. The NADPH oxidases are considered “master oxidases” that direct the activity of other sources of ROS, and when the NADPH oxidases are activated, they lead to formation of ROS by these other

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sources in a feed forward fashion. There is increasing evidence that the mitochondria are major sources of ROS in hypertension. Angiotensin II-treatment of endothelial cells increases mitochondrial ROS production. Treatment with an SOD mimetic that concentrates in the mitochondria prevents angiotensin II-induced hypertension and reverses it once it is established. Genetic overexpression of either manganese superoxide dismutase (MnSOD) or thioredoxin-2, which reside in the mitochondria, also prevents hypertension in mice.

The mechanisms by which ROS produce hypertension remain an area of substantial investigation. In the vasculature, ROS promote vasoconstriction and vascular remodeling, increasing systemic vascular resistance; a common finding in most cases of human hypertension. ROS in the kidney can increase afferent arteriolar tone and reduce glomerular filtration. ROS can also contribute to glomerular damage. In the distal nephron, ROS enhance activity of the furosemide-sensitive Na/K/2Cl co-transporter and thus reuptake of salt, promoting hypertension.

A major effect of ROS is to modulate signaling within the central nervous system. In particular, circulating angiotensin II can stimulate NADPH oxidases in the circumventricular organs (CVO), which have a poorly developed blood brain barrier. The consequent increase in ROS in the CVO promotes excitability of neuronal cells and ultimately increases sympathetic outflow.

Despite the wealth of literature supporting a role of oxidative stress in experimental hypertension, the evidence that oxidative stress contributes to hypertension in humans is not convincing. Several studies have shown that hypertensive humans have increased markers of oxidative stress, such as urinary isoprostanes, malondialdehyde and 8-hydroxy-2 guanosine, and that these are reduced by treatment with various antihypertensive agents. These parameters of oxidant stress could be elevated due to hypertension rather than be a cause of the disease. Several small studies have examined the ability of antioxidants to lower blood pressure, with generally negative results. In an initial small study, vitamin C supplementation lowered blood pressure, however subsequent studies have not confirmed this benefit. The large Su.Vi.Max study of 5086 individuals showed an inverse relationship between plasma beta carotene and the development of hypertension over 6.5 years, but found no effect of supplementation with various antioxidants on development of hypertension during this observation time. Recent studies of vitamin supplementation have shown no benefit in treatment of pre-eclampsia and a hint of increase in gestational hypertension. In one small study of patients with type 2 diabetes, vitamin E supplementation for 6 weeks paradoxically increased diastolic and systolic pressures by 5 to 7 mmHg as measured by ambulatory blood pressure monitoring. Taken together, there seems to be minimal to no benefit of antioxidant therapy in the treatment or prevention of hypertension. These findings are in keeping with several large studies in atherosclerosis, showing no benefit of vitamin E, and some hint of harm of this supplement.

In light of the overwhelming amount of experimental data supporting a role of oxidant stress in hypertension and other cardiovascular diseases, one must ask why the clinical studies of antioxidants have been so disappointing. There are many explanations for this quandary. One is that the oxidative stress hypothesis for human hypertension and related diseases is

simply wrong. Given the complexity of human hypertension, it is simplistic to assume that oxidative stress is its only cause. Another is that the so-called antioxidants used in these various trials are extremely weak and ineffective. These vitamins have rate constants for reaction with various ROS that are thousands of times slower than the rate constants for ROS with endogenous enzymes, such as superoxide dismutase, catalase and glutathione peroxidase. This makes it highly dubious that addition of a small amount of an orally available antioxidant could do anything to ameliorate oxidant stress. Related to this, as discussed above, oxidant stress can be highly localized to subcellular components, and the commonly employed antioxidants unlikely reach these sites. In addition, it is now clear that ROS have important signaling mechanisms that are essential for cell survival. Thus, non-specific removal of ROS could actually be harmful. This might explain the untoward effects of antioxidants in some studies. Finally, it is quite likely that therapies directed toward inhibiting sources of pathological ROS might be more effective than efforts to scavenge ROS once they are formed. In this regard, therapeutic options already available, such as inhibition of angiotensin II, aldosterone blockade and statin therapy are known to have antioxidant effects by inhibiting activation of ROS-producing enzymes.

Suggested Reading

1. Harrison DG, Gongora MC. Oxidative stress and hypertension. *Med Clin North Am.* 2009; 93:621–635. [PubMed: 19427495]
2. Gill PS, Wilcox CS. NADPH oxidases in the kidney. *Antioxid Redox Signal.* 2006; 8:1597–1607. [PubMed: 16987014]
3. Drummond GR, Selemidis S, Griendling KK, Sobey CG. Combating oxidative stress in vascular disease: NADPH oxidases as therapeutic targets. *Nat Rev Drug Discov.* 2011; 10:453–471. [PubMed: 21629295]
4. Czernichow S, Bertrais S, Blacher J, Galan P, Briancon S, Favier A, Safar M, Hercberg S. Effect of supplementation with antioxidants upon long-term risk of hypertension in the SU.VI.MAX study: association with plasma antioxidant levels. *J Hypertens.* 2005; 23:2013–2018. [PubMed: 16208143]
5. Basaran A, Basaran M, Topatan B. Combined vitamin C and E supplementation for the prevention of preeclampsia: a systematic review and meta-analysis. *Obstet Gynecol Surv.* 2010; 65:653–667. [PubMed: 21182804]
6. Widder JD, Harrison DG. Can vitamin E prevent cardiovascular events and cancer? *Nat Clin Pract Cardiovasc Med.* 2005; 2:510–511. [PubMed: 16186847]
7. Dikalova AE, Bikineyeva AT, Budzyn K, Nazarewicz RR, McCann L, Lewis W, Harrison DG, Dikalov SI. Therapeutic targeting of mitochondrial superoxide in hypertension. *Circ Res.* 2010; 107:106–116. [PubMed: 20448215]
8. Ward NC, Wu JH, Clarke MW, Puddey IB, Burke V, Croft KD, Hodgson JM. The effect of vitamin E on blood pressure in individuals with type 2 diabetes: a randomized, double-blind, placebo-controlled trial. *J Hypertens.* 2007; 25:227–234. [PubMed: 17143195]
9. Duffy SJ, Gokce N, Holbrook M, Huang A, Frei B, Keaney JF Jr, Vita JA. Treatment of hypertension with ascorbic acid. *Lancet.* 1999; 354:2048–2049. [PubMed: 10636373]

1. Oxidative stress is defined as:
 - a. An overproduction of antioxidant enzymes.
 - b. A reduction in production of reactive oxygen species.
 - c. A situation in which the production of reactive oxygen species exceeds the antioxidant capacity of a cell or organism.
 - d. A loss of glutathione in a cell.
2. Sources of reactive oxygen species in mammalian cells include:
 - a. The NADPH oxidase, xanthine oxidase and superoxide dismutase.
 - b. Glutathione, uncoupled nitric oxide synthase and the mitochondria.
 - c. The NADPH oxidase, xanthine oxidase, uncoupled nitric oxide synthase and the mitochondria.
 - d. Catalase, uric acid and superoxide.
3. Antioxidant defenses in mammalian cells include:
 - a. Superoxide dismutase, catalase, glutathione peroxidases, thioredoxins and small molecules such as glutathione and uric acid.
 - b. Superoxide, catalase, the NADPH oxidase and xanthine oxidase.
 - c. The mitochondria, the nucleus and the endoplasmic reticulum.
 - d. Superoxide dismutase, uncoupled nitric oxide synthase, catalase and oxidized glutathione.
4. The production of reactive oxygen species occurs:
 - a. Globally at the same level of output throughout the cell.
 - b. Only in the mitochondria.
 - c. In the cell nucleus as a product of DNA transcription.
 - d. Can occur locally within various organelles and can cause oxidant stress locally at these sites.
5. By which of the following mechanisms can angiotensin II increase production of reactive oxygen species?
 - a. Stimulation of the NADPH oxidase.
 - b. Increase in expression of superoxide dismutase.
 - c. Increasing mitochondrial levels of thioredoxin.
 - d. Stimulation of vascular smooth muscle hypertrophy.
6. In the vasculature, ROS have which of the following effects:
 - a. Inhibit vascular smooth muscle motility.

- b.** Promote vascular smooth muscle hypertrophy and produces vasoconstriction.
 - c.** Enhance the half-life of endothelium-derived nitric oxide.
 - d.** Reduce activity of xanthine oxidase.
- 7.** In the kidney, which of the following are known actions of reactive oxygen species that could promote hypertension:
- a.** Promote afferent arteriolar vasoconstriction, enhance sodium reabsorption in the distal nephron and cause glomerular damage.
 - b.** Promote afferent arteriolar vasoconstriction, enhance pressure natriuresis and cause glomerular damage.
 - c.** Promote afferent arteriolar vasoconstriction, enhance sodium reabsorption in the distal nephron and stimulate glomerular filtration.
 - d.** Promote efferent arteriolar vasodilation, enhance sodium reabsorption in the distal nephron and cause glomerular damage.
- 8.** Which of the following are true regarding the role of reactive oxygen species in the central nervous system:
- a.** Neuronal cells do not produce reactive oxygen species.
 - b.** Angiotensin II circulating in the blood directly acts on nuclei in the brainstem to promote ROS production, leading to hypertension.
 - c.** The circumventricular organs include the rostral ventral lateral medulla, the paraventricular nucleus and the Pons.
 - d.** Circulating angiotensin II acts on the circumventricular organs (CVO) to stimulate ROS production. ROS production in the CVO promotes neuronal firing, leading to increased sympathetic outflow.
- 9.** Which of the following is true regarding the oxidant stress and human hypertension:
- a.** Antioxidant vitamin treatment has proven highly effective in prevention or treatment of human hypertension.
 - b.** The correct dose of antioxidants for treatment of hypertension is 1000 mg of vitamin C and 1000 IU per day. This dose should be reduced in women < 60 kg.
 - c.** Antioxidant therapy has prevented untoward outcomes in pre-eclampsia.
 - d.** Antioxidant therapies have had paradoxically increased blood pressure in one study of patients with type 2 diabetes.
- 10.** Which of the following are true regarding future considerations of antioxidant therapies in cardiovascular diseases:

- a.** The oxidant stress concept of hypertension is unequivocally correct and therefore we simply need to find better antioxidants.
- b.** The currently available antioxidants are highly effective in removing reactive oxygen species in humans.
- c.** Removal of all reactive oxygen species is highly desirable, because this enhances telomere length and prolongs life indefinitely.
- d.** Currently available antioxidants, including vitamin C and E are not recommended in the treatment of hypertension or other cardiovascular disease.

Figure.

Sources and actions of reactive oxygen species (ROS) in hypertension: ROS including superoxide, hydrogen peroxide and others are produced by sources including the mitochondria, uncoupled nitric oxide synthase, the NADPH oxidase and xanthine oxidase. ROS have myriad effects on the vasculature, the kidney and the brain. In the vasculature, ROS promote vasoconstriction and vascular hypertrophy. In the kidney, ROS cause afferent arteriolar vasoconstriction, which reduces GFR. ROS also increase sodium reabsorption in the distal nephron and affect tubuloglomerular feedback. In the brain, ROS formed in several nuclei enhance sympathetic outflow. The circumventricular organs (CVO), which receive signals from circulating hormones such as angiotensin II, include the subfornical organ (SFO), the median pre-optic eminence (MPO) and the organum vasculosum of the lateral terminalis (OVLT) and the area postrema (AP). The paraventricular nucleus (PVN) communicates with these CVO and sends projections to the posterior pituitary (shown in green) to modulate vasopressin and oxytocin release. Signals from the CVO interact with regions in the brainstem, including the nucleus tractus solitarius (NTS) and the ventral lateral medulla (VLM) to modulate sympathetic outflow. Also shown is the parabrachial nucleus (PBN) of the Pons.