Oxidative stress: does it play a role in the genesis of essential hypertension and hypertension of uraemia?

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Reactive oxygen species: general aspects

Reactive oxygen species, including superoxide radicals, hydrogen peroxide, nitric oxide, peroxynitrite, hydroxyl radicals and hypochlorous acid are by-products of normal metabolic processes in cells. Reactive oxygen species can be found in several cells including macrophages and vascular smooth muscle cells. At low concentrations reactive oxygen species can act as physiological mediators of cellular responses whereas higher concentrations may cause cell damage [1,2]. The major sources of reactive oxygen species are leakages from the electron transport chains of mitochondria and endoplasmic reticulum. Cellular energy metabolism is based on the production of ATP through the electron transport reaction in which O₂ accepts electrons and H⁺ and then is eventually reduced to water. Only 1–2% of the electrons are leaked to generate superoxide radicals in reactions mediated by coenzyme Q and ubiquinone and its complexes. During ageing (and probably in patients with hypertension and/or atherosclerosis) respiratory function declines and results in enhanced production of reactive oxygen species in mitochondria whereas the activities of free radical scavenging enzymes are reduced. In turn, reactive oxygen species induce stress responses by altering expression of respiratory genes to uphold the energy metabolism to rescue the cell [3]. Neutrophils and macrophages produce reactive oxygen species during phagocytosis (‘oxygen burst’) or stimulation with several agents through the activation of nicotinamide adenine dinucleotide phosphate reduced [NAD(P)H] oxidase that is assembled at the plasma membrane from resident plasma membrane components and cytosolic protein components [4]. The NAD(P)H oxidase is also the major source of vascular superoxide production. Vascular NAD(P)H oxidase contains the plasma membrane components gp91phox-homologues (nox1, nox4 or gp91phox) and p22phox, and the cytosolic protein components p47phox and p67phox [5]. It should be noted that the activation of vascular NAD(P)H oxidase by angiotensin II stimulates both superoxide production and NO production, thereby increasing peroxynitrite formation [6]. Endothelial nitric oxide synthase [7], inducible nitric oxide synthase [8] and xanthine oxidase [9] are other sources of superoxide radicals. After activation of vascular NAD(P)H oxidase (for example, by angiotensin II, thrombin, platelet-derived growth factor and others) the production of reactive oxygen species depends on activation of several intracellular signalling pathways including protein kinase C, the upstream activator of epidermal growth factor receptor, c-src, epidermal growth factor receptor transactivation, phosphatidylinositol-3-kinase and rac, a small molecular weight G protein. Several cellular signalling molecules such as protein tyrosine kinases, serine/threonine kinases, phospholipase C or cytosolic calcium are modified by reactive oxygen species. Reactive oxygen species activate protein tyrosine kinase pathways including epidermal growth factor receptor, insulin receptor, and platelet-derived-growth-factor receptor [10,11]. Reactive oxygen species activate extracellular signal-regulated kinases through c-src and ras [12]. Reactive oxygen species activate serine/threonine kinases including mitogen-activated protein kinase, p39 mitogen-activated protein kinase, Akt and protein kinase C [13,14].

Reactive oxygen species and hypertension in the absence of renal failure

There are several pieces of experimental evidence that increased oxidative stress contributes to the pathogenesis of hypertension. Hypertensive Dahl rats had significantly higher plasma hydrogen peroxide concentrations and superoxide radicals in
microvessels of the mesentery compared to their normotensive counterparts [15]. Spontaneously hypertensive rats showed higher blood pressure and increased excretion of 8-iso prostaglandin F2alpha, which is thought to be formed nonenzymatically from the attack of superoxide radical on arachidonic acid. Long-term administration of superoxide scavenger tempol in the drinking water for 2 weeks reduced blood pressure and excretion of 8-iso prostaglandin F2alpha. These data indicate that superoxide radicals contribute to the development of hypertension in such rats [16]. The oral administration of buthionine sulfoximine, an inhibitor of glutathione synthase, to Sprague-Dawley rats increased blood pressure, reduced antioxidative tissue glutathione content, and increased tissue nitrotyrosine abundance, a marker of NO inactivation by reactive oxygen species. These data indicate that increased oxidative stress after glutathione depletion causes hypertension [17]. In the kidneys of spontaneously hypertensive rats an increase in p47phox and p67phox expression could be detected [18]. Angiotensin II infusion increased blood pressure and superoxide radical production in rats. The p22phox expression and NAD(P)H oxidase activity in rat aorta were increased in angiotensin II-induced hypertension [19]. Interestingly, the hydroxymethylglutaryl-coenzyme A reductase inhibitor, simvastatin, prevented the development of hypertension together with the inhibition of reactive oxygen species production in Sprague-Dawley rats infused with angiotensin II [20]. Angiotensin II infusion for 7 days increased systolic blood pressure in six wild-type mice from 105 ± 2 to 151 ± 6 mmHg and increased vascular superoxide radical production. On the other hand, angiotensin II infusion in six p47phox-deficient mice increased systolic blood pressure only from 96 ± 6 to 122 ± 4 mmHg without changing vascular superoxide radical production. These data indicate that angiotensin II-induced hypertension in mice depends at least partially on the presence of the p47phox subunit of NAD(P)H oxidase [21].

In humans, multiple regression analysis showed a significant correlation between mean blood pressure and oxidative stress in polymorphonuclear leucocytes [22]. In human internal mammary arteries and saphenous veins the administration of apocynin, an inhibitor of NAD(P)H oxidase that impedes assembly of the p47phox subunit with the membrane complex, reduced superoxide radical generation and caused vasorelaxation [23]. The endothelium-dependent acetylcholine-induced vasodilation was significantly reduced in patients with essential hypertension compared to normotensive control subjects. The administration of vitamin C enhanced the acetylcholine-induced vasodilation in hypertensive patients aged >30 years. These data point to the role of increased reactive oxygen species and vasoconstriction in patients with essential hypertension due to endothelial dysfunction and/or reduced vasodilator activity [24]. The response of forearm blood flow to acetylcholine, an endothelium-dependent vasodilator, was significantly improved after renal artery angioplasty in patients with renovascular hypertension. Angioplasty decreased systolic and diastolic blood pressure, plasma renin activity and plasma angiotensin II levels, serum malondialdehyde-modified low density lipoprotein, and urinary excretion of 8-hydroxy-2-deoxyguanosine, indicating that oxidative stress is increased in patients with renovascular hypertension [25].

**Reactive oxygen species and hypertension in uraemia**

Several studies have revealed evidence of increased oxidative stress in chronic renal failure. Increased reactive oxygen species [26], elevated plasma lipid oxidation products, increased F2-isoprostanes, which are products of radical-induced peroxidation reactions of arachidonic acid, increased plasma protein 3-chlorotyrosine, a biomarker of myeloperoxidase-catalysed oxidation, depressed antioxidant capacity including impaired antioxidative enzyme systems have been reported in chronic renal failure [27]. Hypertension is a common complication of chronic renal failure. Renal hypertension may be caused by several factors including extracellular fluid volume expansion, increased sympathetic activity, elevated endothelin production, enhanced local or systemic renin–angiotensin system activity, and accumulation of Na,K-ATPase inhibitors and Ca2+-ATPase inhibitors (Figure 1).

Several experimental data indicate that increased oxidative stress contributes to hypertension in uraemia. In the kidney from 5/6 nephrectomy rats increased gp91phox could be detected [28]. The administration of lazaroid, a lipid peroxidase inhibitor, for 2 weeks ameliorated the elevation of blood pressure and malondialdehyde in 5/6 nephrectomy rats. Interestingly, no discernible effects were found with either administration of superoxide dismutase or catalase (superoxide and hydrogen peroxide quenchers), whereas dimethylthiourea, a known inhibitor of endoplasmic Ca2+-ATPase and scavenger of hydroxyl radicals, also reduced blood pressure in 5/6 nephrectomy rats. These data suggest that increased hydroxyl radicals, but not superoxide or hydrogen peroxide, in chronic renal failure are involved in renal hypertension [29]. The administration of a superoxide scavenger, tempol, in the drinking water for 1 week ameliorated hypertension and reduced tissue nitrotyrosine abundance (as determined by western blot) in 5/6 nephrectomy rats [28]. In another study, the administration of tempol for 10 days prevented the increase of systolic blood pressure, and exogenous superoxide dismutase improved the decreased response to acetylcholine in isolated mesenteric arteries from 5/6 nephrectomy rats [30].

In humans, acetylcholine-induced vasodilation has been shown to be reduced in resistance vessels of subcutaneous fat biopsies from patients with end-stage renal failure [31]. Measurements of blood flow using forearm plethysmography showed reduced
vasodilation in response to carbachol (endothelium-dependent vasodilator) in both pre-dialysis patients and uraemic patients on continuous ambulatory peritoneal dialysis with a preserved response to sodium nitroprusside (endothelium-independent vasodilator) [32]. The endothelium-dependent vasodilation evaluated by forearm blood flow measurements with venous occlusion plethysmography during local intra-arterial infusions of methacholine was significantly reduced in patients with chronic renal failure compared to controls [33].

In conclusion, oxidative stress is an important pathogenic factor in patients with impaired renal function that at least partially causes uraemic hypertension.

References


Ageing, hypertension and the kidney: new data on an old problem

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Introduction

End-stage renal disease (ESRD) has become an increasingly common health problem, even for the elderly, especially in the developed countries [1–3]. From 1997 to 2000, the incidence rate of ESRD among patients aged 65 to 74 and those ≥75 years old has increased to 7.8% and 22.3%, respectively, in the United States [1]. The leading causes of ESRD are diabetes mellitus and hypertension, and hypertension is a very frequent co-morbid condition of diabetes. Both are exceedingly common in the elderly, and they dramatically exacerbate ESRD development [4]. Of particular interest is that experimental studies in recent years have shown similar renal haemodynamic, glomerular dynamic, renal functional and histopathological changes in both diabetic nephropathy and hypertensive renal injuries [5–8]. These pathophysiological alterations are characterized by diminished renal blood flow and increased renal...


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