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Angiotensin II-dependent superoxide: effects on hypertension and vascular dysfunction

William J Welch
Department of Medicine, Georgetown University, 4000 Reservoir Road, Building D-395, 202 687-4082, FAX 202 687-4194, welchw@georgetown.edu

Introduction

Angiotensin II generates reactive oxygen species (ROS) by activation of angiotensin II type 1 receptors (AT_1-R). The resulting ROS mediates many of the actions of Ang II, including constriction of vascular smooth muscles, increased systemic blood pressure, endothelial dysfunction, vascular remodeling and sodium retention. Ang II has its greatest effect on superoxide anion (O_2^-), which may be an important signaling element of the hypertensive and other deleterious actions of Ang II. The mechanisms of ROS actions are not fully understood, yet effective antioxidant therapy often attenuates hypertension and other vascular effects of Ang II. Currently many studies use Ang II-infused animal models to investigate the role of ROS and interacting systems, not only on hypertension, but endothelial dysfunction, renal disease, heart disease and other pathologies. This review will focus on the recent progress on Ang II generated ROS and how it impacts hypertension and its vascular consequences.

Mechanism of Ang II generation of O_2^-

Superoxides are formed by several oxidases and oxygenases, and incomplete mitochondrial oxidative phosphorylation. The major source of O_2^- that impacts the vasculature and systemic blood pressure is NADPH oxidase, which is abundantly expressed in vascular smooth muscle cells. Five isoforms of NADPH oxidase (Nox) have been identified in animals: Nox1-5, with Nox1, Nox2 and Nox4 expressed in vascular cells. Nox isoforms are composed of 2-5 subunits: 2 membrane-bound subunits: $gp91^{phox}$ and $p22^{phox}$, and cytosolic subunits $p47^{phox}$, $p67^{phox}$, and Rac-1 (reviewed in Mehta and Griendling[1]). Ang II upregulates several subunits of NADPH oxidase, however most evidence suggests that assembly of NADPH oxidase onto cell membranes is initiated by Rac-1, which is activated by Ang II binding to AT_1-R. However alternate pathways continue to be explored. O_2^- generated by Nox is metabolized by superoxide dismutases (SOD) to form hydrogen peroxide (H_2O_2) or is scavenged by nitric oxide (NO) forming peroxynitrite ($ONOO^-$). In addition, H_2O_2, is subsequently further reduced by catalase or glutathione peroxidase. Interaction with these important metabolic pathways also determines the physiological effects of Ang II-generated O_2^-.

Transfection studies have linked Ang II with Nox isoforms. Nox1 and Nox2, as well as isoforms of $p47^{phox}$ and $p67^{phox}$, NoxO1 and NoxA1 were transfected into cultured human embryonic kidney (HEK293) cells prior to Ang II exposure. Ang II increased both Nox1 and Nox2 activity which was linked to intermediates Gα(q/11), phospholipase C-β and protein kinase C (PKC).[2] Maximal activity of Nox1 required NoxO1 and NoxA1, and Nox2 required $p47^{phox}$ and $p67^{phox}$. Ang II effects on Nox2 were more predominant and required additional pathways, including PI-3 kinase and Rac1, which confirms earlier studies.[3]

Disclosures: None

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Signaling by Ang II to NADPH oxidase may also require the extracellular signaling-regulated kinase 1/2 (ERK1/2)-mitogen-activated protein kinase (MAPK) pathways. In aortas harvested from Ang II infused rats, O_2^-, ERK1/2 phosphorylation and spontaneous tone were enhanced compared to control aortas. Specific inhibitors to MAPK/ERK1/2 reduced all of these effects. This suggests that the vasoconstriction associated with O_2^- derived from Ang II stimulation requires this important signaling process.[4]

The epithelial transcription factor-1 (Ets-1) may also be part of the signaling process in Ang II stimulated O_2^- production. O_2^- was lower in the thoracic aorta from Ets-1 (-/-) mice treated with Ang II than in WT tissue. In cultured human aortic smooth muscle cells, siRNA to Ets-1 reduced O_2^- production and induction of $p47^{phox}$ by Ang II, confirming the in vivo results.[5]

Blood pressure effects of Ang II-O_2^-

Though several Nox isoforms are involved in generation of Ang II-dependent O_2^-, their role in the development of Ang II-dependent hypertension is less clear. Many studies have linked Ang II with vascular NAPDH oxidase, based on inhibition by apocynin. However, a recent study showed that apocynin requires activation by myeloperoxidase (MPO) to inhibit NAPDH oxidase. MPO is expressed in leukocytes, but not in cultured vascular cells, suggesting studies that have identified vascular Nox-dependent effects of Ang II based solely on the use of apocynin may need to be reconsidered.[6] Yet apocynin is an effective antioxidant and remains useful in identifying links between Ang II and O_2^-. Further complicating this issue are recent studies using more specific genetic tools such as single gene deficient mouse models that have shown conflicting results. Separate reports show that Nox-1 or $gp91^{phox}$ knockout mice have similar BP, but differ in responses to Ang II. Matsuno et al showed that Ang II infusion increased BP less in Nox1 knockout mice than in wild type mice.[7] However, in Nox1 knockout mice crossbred with transgenic mice expressing human renin (TTRhRen), which had high circulating Ang II, BP was similar to control mice.[8]

Conversely, overexpression of Nox increases BP responses to Ang II. When Nox2 was overexpressed in mice, acute and chronic infusion of Ang II increased BP more in transgenic mice compared to wild type.[9] Similarly, Nox-1 overexpression lead to greater increases in BP, O_2^- production and smooth muscle hypertrophy compared to control mice.[10] In addition, tempol partially attenuated the increases in BP, O_2^- and hypertrophy.[10]

These conflicting results may be due to differences in study designs comparing acute and chronic reduction of Nox. In Ang II-infused studies, the acute or short-term role of O_2^- in the development of hypertension has been shown in multiple studies, whereas compensation of the loss of O_2^- in chronic lifetime genetic models may masks its role. Alternately, high Ang II over a lifetime can increase BP and subsequent end-organ damage by other mechanisms, independent of O_2^-.

Using a different molecular strategy, Modlinger et al showed that reduction of $p22^{phox}$, a subunit of multiple Nox isoforms, by small interfering RNA ameliorated Ang II-dependent increased BP.[11] The Ang II-dependent hypertension, measured by radiotelemetry was diminished by injection of siRNA directed to $p22^{phox}$ in adult rats. The siRNA treated rats also had lower levels of isoprostane excretion.[11]

Another consideration is the effect of hypertension on O_2^- production, independent of Ang II. Other forms of hypertension such as high salt intake or deoxycorticosterone (DOCA) infusions also increase O_2^-.[12,13] However, studies cited above with Ang II infusion resulting in high circulating Ang II sufficient to increase BP show that BP was reduced by targeting Nox sources of O_2^- or O_2^- scavenging.[8-11] Relevant to this issue is the study by Jalil et al, who showed that Brown Norway (BN) rats have elevated angiotensin converting enzyme and circulating Ang

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II without hypertension.[14] However, O_2^- production was higher in aorta from BN rats compared to those from the control Lewis rats and was substantially reduced by candesartan, an AT_1-R antagonist. This observation suggests that Ang II-linked O_2^- is not dependent on increased BP.[14]

Ang II-O_2^- effects in the heart

Cardiac hypertrophy generated by Ang II-dependent hypertension may also be due to increased O_2^-. Kobayashi et al [15] studied the effects of carbon monoxide (CO) since it reduces O_2^- and may ameliorate the prooxidant effects of Ang II. In Ang II-infused mice, CO administered for 2 hours per day, attenuated the rise in BP and left ventricular hypertrophy (LVH) compared to Ang II controls. Multiple parameters of ROS were also reduced by CO treatment. Hydralazine, used as a control that did not alter CO, lowered BP in Ang II treated mice but was less effective in reducing LVH and ROS. These authors conclude that CO acts via reduction in Ang II-dependent NADPH oxidase activity.

To examine the mechanism of cardiac hypertrophy, Ang II was exposed to primary rat cardiomyocytes.[16] Ang II increased Rac1 activation, O_2^- production and cell size, which were blocked by adenoviral introduction of dominant-negative Rac1 and CuZn-SOD and by siRNA directed to Nox-2. These results suggest that Ang II activation of Nox-2 contributes to cardiac hypertrophy.

In an interesting study that suggests an important protective role of Ang II-generated O_2^-, cardiac damage following ischemia/reperfusion was attenuated by Ang II preconditioning.[17] This appears to be mediated by both mitochondrial and NADPH oxidase generated O_2^-, since the reduced infarct size was abolished by inhibition of both sources. In addition the expression of NAPDH oxidase subunits and activity of NADPH oxidase were attenuated by Ang II preconditioning, suggesting that mitochondrial ROS are stimulated by cytosolic oxidases.

Not all recent studies have confirmed that Nox is linked to Ang II damage. Touyz et al showed that chronic Ang II-dependent cardiac hypertrophy was not altered in $gp91^{phox}$ (Nox1) knockout mice.[18]

Vascular effects of Ang II-O_2^-

Several recent studies have linked the endothelial dysfunction, inflammation and excess vasoconstriction of Ang II to NAPDH oxidase and other sources of O_2^-. In the low renin model of Dahl salt-sensitive (DS) hypertension, reduction of $gp91^{phox}$ with $gp91^{phox}$-tat, reduced ROS production, improved endothelium-dependent relaxation and lowered inflammatory precursors, without a significant effect on BP.[19]

In a model of Ang II-dependent hypertension generated by overexpression of the mouse renin transgene in rats suggest that vascular injury is mediated by increased O_2^- production.[20] In these transgenic rats with substantially elevated Ang II, endothelial dysfunction, inflammation, insulin resistance and vascular NADPH oxidase were all increased. Treatment with valsartan, an AT_1-R antagonist or tempol, a superoxide dismutase (SOD) mimetic, attenuated all parameters. However, in this model of malignant hypertension, tempol did not have a significant effect on blood pressure, whereas valsartan normalized BP.

Aortic dissection and aneurysm formation is another consequence of endothelial dysfunction during hypertension. Seven days of Ang II infusion induced aortic dissection in 23% of wild type mice, but only 4% of Nox1-deficient mice.[21] This study was particularly interesting since norepinephrine failed to generate aortic dissection, confirming the selective role of Ang II on NADPH oxidase.

Ang II also induces abdominal aortic aneurysms (AAA). To test the role of O_2^-, AAAs were assessed in apoE (-/-) mice and crossbred apoE(-/-) and $p47^{phox}$ (-/-) mice, following 4 weeks of Ang II infusion. Ang II induced AAA in 90% of apoE(-/-), but only 16% of apoE(-/-)/ $p47^{phox}$(-/-) mice. In addition the Ang II pressor response was lower in apoE(-/-)/$p47^{phox}$(-/-) compared to apoE(-/-) mice. As seen above, norepineprhine infusion did not generate AAA or elevated O_2^-.[22]

Most studies have shown that NADPH oxidase is the major source of Ang II-dependent ROS, however the mitochondrion is also a major source of O_2^-. Mitochondrial O_2^- was increased by Ang II in rat vascular smooth muscle cells (RVSMC) and in the rat aorta. However, inhibition of mitochondria O_2^- by a specific ATP-sensitive potassium channel blocker had no effect on calcium mobilization in RVSMC or altered BP in Ang II-infused rats.[23] These data suggest that Ang II derived O_2^- sufficient to alter vascular tone and hypertension is independent of mitochondrial O_2^-, which confirms earlier work identifying NADPH oxidase as the major source.

Vascular injury caused by Ang II could be due to increased apoptosis. In the rat carotid artery and in cultured endothelial cells, Ang II and H_2O_2 increased indices of apoptosis and isoprostane production, a marker of O_2^-. Specific inhibition of AT_1-R reduced apoptosis and isoprostane production.[24]

AT_1-R blockers also reduced atherosclerosis and NADPH oxidase activity in ApoE knockout mice, with less modest effects in female mice. Addition of estrogen (17-β estradiol) enhanced the anti-atherosclerotic actions of olmesartan via its effects on O_2^- production.[25] These data suggest that estrogen provides additional protection against excess O_2^-.

Vascular hypertrophy and aortic O_2^- production in mice are increased following 2 weeks of Ang II infusion. However, in mice in which catalase has been overexpressed only in vascular smooth muscle, thus reducing vascular H_2O_2 levels, hypertrophy was substantially attenuated.[26] BP was not different in catalase-overexpressed mice. Glutathione peroxidase (Gpx) metabolizes H_2O_2 providing vascular protection against this ROS. Carotid arteries from Gpx (-/-) mice were less responsive to relaxation induced by acetylcholine (ACh), an endothelium-dependent agonist, than wild type arteries.[27] In vitro exposure to Ang II also impaired relaxation to ACh in arteries from Gpx (-/-), whereas Ang II had no effect on arteries from Gpx transgenic mice. This suggests that H_2O_2 mediates Ang II-induced endothelial dysfunction and that under normal conditions Gpx protects the vessels.

Ang II stimulates multiple inflammatory pathways, however a recent study suggests that IL-6 is required for maximal O_2^- production in vessels. Carotid arteries from IL-6 deficient mice had less hypertrophy and endothelial dysfunction compared to wild type tissue. Stimulation of vascular superoxide and IL-6 by Ang II was absent in IL6 (-/-) mice.[28]

Conversely Ang II induces IL-6 via mineralocorticoid receptors in humans and may be independent of O_2^-. Human subjects were infused for 3 hours with low doses of Ang II, which increased plasma IL-6, but not after treatment with spironolactone. Spironolactone had no effect on Ang II stimulation of F2-isoprostanes, suggesting that this intervention did not alter O_2^- production.[29]

Neural effects of Ang II-O_2^-

Hypertension is also linked to increased brain levels of Ang II, which mediates its effects partially via O_2^- and intracellular Ca^{++} changes. To examine this relationship, neuroblastoma cells were exposed to Ang II, which increased voltage-sensitive $[Ca^{++}]i$. This effect was attenuated by overexpression of CuZnSOD in these cells, which increased O_2^- scavenging, and

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by expression of dominant-negative isoform of Rac1, preventing formation of NAPDH oxidase by Ang II.[30]

Similar roles for Ang II and O_2^- have been explored in the nuclear tractus solitarius (NTS), which is an important site for cardiovascular regulation by the brain. Suppression of NADPH oxidase in the NTS by transfection of adenoviral vectors for dominant-negative Rac-1 reduced Ang II-dependent BP by 20-30 mmHg.[31] This supports and confirms earlier studies in the aorta and kidney on the critical role of Rac-1 signaling in stimulation of NADPH oxidase.[32] Changes in Ca^{++} currents in the brain are also regulated by Ang II and therefore may require O_2^-. In a study using isolated NTS, Nox2 was required to show increased O_2^- production and enhanced Ca^{++} current in response to Ang II.[33] This pathway was linked to PKC, since specific inhibition also suppressed Ca^{++} responses to Ang II.

The β−1 receptor antagonist, nebivolol has vasodilating and antioxidant properties. In Ang II-dependent hypertensive rats, nebivolol prevented vascular endothelial dysfunction, reduced O_2^- production and enhanced bioavailable NO.[34] This powerful antioxidant effect of nebivolol is related to its ability to prevent assembly of NAPDH oxidase, demonstrated in cultured cells.

Sympathetic-initiated vasoconstriction in exercising muscle is attenuated by locally produced NO. However in Ang II-infused rats, sympathetic stimulation of femoral conductance was greater compared to control responses and was attenuated by the O_2^- scavenger tempol. This suggests that during high Ang II conditions, increased O_2^- activity leads to greater vasoconstriction in exercising muscle.[35]

Ang II-O_2^- in the Kidney

The kidney is a rich source of NADPH oxidase, which is stimulated by Ang II and linked to renal vasoconstriction, renal failure and tubular function. Ang II increased DNA damage assessed in pig kidney cells (LLC-PK1) 6-15-fold. This was prevented by AT_1-R, but not by AT_2-R blockers. The antioxidants N-acetlycysteine and α-tocopherol also attenuated the effects of Ang II.[36]

The increase in NADPH oxidase by Ang II also impacts podocyte function, increasing inflammation and reducing filtration, further contributing to renal-based hypertension. In the renin transgenic rat, with high circulating Ang II, oxidative stress was attenuated by statin treatment resulting in less podocyte damage.[37] In addition to their cholesterol-lowering effects, statins also inhibit Rac1 and Nox-dependent O_2^-.

In a model of slowly developing hypertension created by infusion of a low dose of Ang II, mice deficient of extracellular SOD (EC-SOD) had a similar increase in MAP compared to wild type mice. Ang II increased O_2^- production, renal expression of NADPH oxidase and renal vascular resistance. This result suggests that EC-SOD is not a major defense against overproduction of superoxide. However, intracellular-SOD in the kidney was upregulated by Ang II, compensating for the lack of EC-SOD.[38]

Conversely, a high dose of Ang II, which increased BP within 24 hours, had greater effects in EC-SOD KO mice. In mesenteric resistance vessels, Ang II reduced endothelium-dependent vasodilation, as expected. Ang II caused paradoxical increases in endothelium-dependent vasodilation and the authors suggest that increased CuZn-SOD activity in the aorta compensated for the lack of EC-SOD.[39]

Increased Ang II-dependent O_2^- may also alter renal function, possibly contributing to the elevation in BP. In Ang II infused hypertensive rats, acute tempol injections increased renal

blood flow, GFR and Na excretion[40], whereas long-term tempol treatment had no effect on renal function, measured at the end of a 2-week treatment period.[41]

In stroke-prone SHR, renal expression of glutathione *S*-transferase μ type 1 (*Gstm1*) is 4-fold lower than WKY rats, which may contribute to oxidative stress in these rats. *Gstm1* is a major defense enzyme against excess O_2^- production and the authors suggest it may represent a novel candidate for hypertension-associated oxidative stress.[42]

Interactions with other vasoactive systems

Stimulation of O_2^- by Ang II can alter other vasoactive systems and several recent studies have expanded our knowledge of these potentially important interactions.

Cyclooxygenases generate several vasoactive prostaglandins and may promote formation of ROS. Infusion of Ang II in rats increased BP, oxidative stress and cyclooxygenase-2 (COX-2) expression in the aorta and heart.[43] Selective inhibition of COX-2 attenuated the hypertension and oxidative stress, whereas non-selective inflammatory inhibitors had no effect. In the kidney COX-2 may also be regulated by O_2^- from Ang II-NADPH oxidase. COX-2 expression in the renal cortex of Dahl salt-sensitive (DSS) rats on a high salt intake was increased by 2-fold. Inhibition of AT_1-R by daily candesartan treatment restored normal COX-2 expression in DSS.[44]

However, COX-1 may be involved in endothelial dysfunction associated with Ang II-induced hypertension. In mesenteric arteries from Ang II-infused mice, the acetylcholine-induced relaxation was enhanced by a COX-1 inhibitor and by a thromboxane-prostanoid receptor (TPR) antagonist.[45] These effects were prevented by apocynin, suggesting the effects of Ang II to increase COX-1 activity are mediated by NADPH oxidase. Increased COX-1 activity generates thromboxane that increased arterial tone, leading to endothelial dysfunction during Ang II infusion.

The kinin receptor B1 mediates vasodilation and participates in the regulation of vascular tone during hypertension. Ang II infusion for 2 weeks induced B1 receptor in the rat aorta, but this was prevented by co-treatment with apocynin (APO).[46] More importantly, APO did not lower the BP induced by Ang II. This suggests that AT_1-R activation stimulates B1 receptor induction, but only via NADPH oxidase, rather than increased BP. Endothelin is a potent vasoactive hormone, which acts on two distinct receptors (ET_A, ET_B) and can increase vascular tone. Plasma endothelin levels are often increased by Ang II. SHR, a model of oxidative stress has higher plasma endothelin levels, which may contribute to the high BP in this strain. To test the role of Ang II on oxidative stress and endothelin, SHR and normotensive rats were treated with captopril for 15 days. BP, markers of oxidant stress and endothelin levels were reduced in SHR, but not in normotensive rats by captopril, suggesting that Ang II stimulation of endothelin is mediated by O_2^-.[47]

Endothelin may also be linked to Ang II signaling in cardiomyocytes. In isolated cardiomyocytes, short-term exposure to Ang II increased positive inotropic effects (PIE), measured by sarcomere shortening, increased O_2^- production and increased ET levels.[48] These effects could be blocked by AT_1-R blockers, antioxidants or the ET_A selective blocker BQ-123. This study suggests that O_2^- activates ET_A without having effects on ET formation.

Ang II also stimulates endothelin in the adventitia, which may contribute to vascular remodeling associated with hypertension. To examine the possible role of O_2^-, cultured mouse adventitial fibroblasts were exposed to Ang II and multiple redox or endothelin inhibitors.[49] Ang II increased endothelin and collagen expression, but NADPH oxidase inhibitors and BQ123.43 attenuated this effect.

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These selected new studies show that O_2^- generated by Ang II may stimulate other vasoactive systems and that these potential interactions are underappreciated.

Summary

There has been substantial progress on understanding the relationship between Ang II, AT_1-R activation and NADPH oxidase production of O_2^-, over the last 2-3 years. Ang II derived O_2^- is recognized as an important signaling component of the classical effects of Ang II. In addition to its contribution to various pathologies, there is emerging evidence that O_2^- mediates normal physiology or can even be protective. The pro-hypertensive and pro-vasoconstrictive mechanisms of O_2^- actions remain less clear. As new information emerges, we will learn how Ang II mediates many of its multiple functions via release of ROS. This new information may lead to the development of antioxidant therapies that will complement Ang II antagonists in the treatment of hypertension and related vascular diseases.

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