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Minireview

Angiotensin II and vascular damage in hypertension: Role of oxidative stress and sympathetic activation

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A B S T R A C T

Reactive oxygen species (ROS) are oxygen derivates and play an active role in vascular biology. These compounds are generated within the vascular wall, at the level of endothelial and vascular smooth muscle cells, as well as by adventitial fibroblasts. Physiologically, ROS generation is counteracted effectively by the rate of elimination. In hypertension, a ROS excess occurs, which is not counterbalanced by the endogenous antioxidant mechanisms, leading to a state of oxidative stress. Angiotensin II, the active peptide of the renin-angiotensin-system (RAS), is a significant stimulus for ROS generation within the vasculature. It was also documented that at the level of subfornical cerebral regions an inappropriate RAS stimulation may lead to an increased vascular sympathetic activity. More recently, in conditions of fetal undernutrition, it was also proposed an increased vascular sympathetic activity secondary to inappropriate RAS activation, leading to the development of hypertension in adult life. The present review will discuss the complex interaction between RAS activation, vascular ROS generation and increased sympathetic outflow in hypertension.

1. Introduction

Increased peripheral vascular resistance due to functional, structural and mechanical changes in small vessels, represents a hallmark of essential hypertension. Functional alterations include an impaired endothelial function secondary to a reduced nitric oxide (NO) availability, while structural changes imply vascular remodelling, resulting from a reduced outer diameter that narrows the lumen without net growth (eutrophic remodelling) or from a thicker media encroaching on the lumen (hypertrophic remodelling) [1]. Vascular fibrosis provides a critical contribution to these vascular structural modifications and involves changes in extracellular matrix components, including collagen type I and III, elastin and fibronectin. In hypertension, media of small arteries is often characterised by increased collagen and fibronectin, as well as a decreased elastin contents [2–4].

Angiotensin (Ang) II is greatly involved in the pathogenesis of microvascular remodelling [5,6]. Ang II can act through two different receptors: Ang II type 1 (AT1) and type 2 (AT2) receptors. While the AT2 expression and activity are very low in adults, the AT1 receptor is ubiquitously expressed in the cardiovascular system and mediates most of the physiological and pathophysiological actions of Ang II. Major mechanisms whereby Ang II exerts vascular remodelling include generation of reactive oxygen species (ROS) and activation of sympathetic nervous system (SNS) activity [7–9].

The present review will focus on Ang II-induced vascular disease in hypertension and the complex interaction between RAS activation, vascular ROS generation and increased sympathetic outflow in hypertension.

2. Vascular reactive oxygen species generation

ROS are reactive derivatives of O_2 metabolism found ubiquitously in the body, including in the cardiovascular system. While maintaining cardiac and vascular integrity in healthy conditions, ROS play a crucial pathophysiological role in several clinical conditions, including hypertension [10,11]. The ROS family encompasses various molecules, including the superoxide anion ($\bullet O_2^-$), hydrogen peroxide, and the reactive nitrogen species peroxynitrite ($ONOO^-$), regarded as life-threatening, and highly destructive oxygen-derived toxicant. Physiologically, ROS generation is tightly regulated by endogenous cellular antioxidants in a fine equilibrium which defines the intracellular redox balance, thus modulating the vascular homeostasis [12].

On the contrary, in different diseases including hypertension, ROS generation exceed the buffering capacities of protective antioxidant mechanisms, leading to a state of oxidative stress [11]. In these conditions, $\bullet O_2^-$ reacts with NO to increase the production of the toxic

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$ONOO^-$ which, in turn, promotes alterations of transcription factors, kinases, protein synthesis, and redox-sensitive genes. These changes in the vascular physiology induce functional alterations, increase vascular contractility, smooth muscle cell growth and apoptosis, monocyte migration, lipid peroxidation, inflammation, and increased deposition of ECM proteins, all major processes deeply involved in the pathogenesis and progression of vascular damage in cardiovascular disease [13,14].

3. Major vascular sources of ROS generation

In hypertension, major sources of ROS are xanthine oxidase, uncoupled endothelial NO synthase (eNOS), nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, cyclooxygenase (COX) and the mitochondrial respiration [15]. The xanthine oxidase system, detectable in the vascular endothelium, catalyses the oxidation of hypoxanthine and xanthine to form $\bullet O_2^-$. Major demonstrations of the role of the xanthine oxidase-system in contributing to the generation of ROS and regulation of the vascular physiology concern the setting of ischemia-reperfusion injury and heart failure. Nevertheless, some experimental reports also suggest the involvement of such complex in hypertension. In small mesenteric vessels from spontaneously hypertensive rats (SHR), an enhanced activity of xanthine oxidase was documented [16]. Beyond its effect within the vascular wall, an active role of xanthine oxidase has also been documented in the kidney from SHR or Dahl salt-sensitive rats. Usually, the xanthine oxidase enzymatic system is inhibited by allopurinol.

The enzymatic system eNOS, constitutively delegated to produce NO, can also generate ROS in those conditions characterised by a deficiency of the substrate arginine [17] or the cofactor tetrahydrobiopterin (BH_4). This process, which has been called "NOS uncoupling", implies that the physiological activity of the enzyme is switched from NO production to the NOS-dependent $\bullet O_2^-$ generation, a condition widely documented in hypertension [18]. eNOS uncoupling has been demonstrated in diabetic and hypertensive patients, where endothelial oxidant excess was dramatically reduced by administration of the precursor of BH_4 [19].

NAD(P)H oxidase represents one of the major sources of $\bullet O_2^-$ in the vasculature, either in the endothelium or in the media and adventitia [13,20]. The activation of such enzymatic system, which utilises NADH/NADPH as electron donor to reduce molecular oxygen and generate $\bullet O_2^-$, requires the assembly of cytosolic (p47phox, p67phox) and membrane-bound (gp91phox/Nox1/Nox4 and p22phox) subunits to form a functional enzyme complex [15]. Within the vascular wall, all the NAD(P)H oxidase subunits are expressed to varying degrees [13,15] and have been involved in the microvascular wall remodelling commonly observed in patients with arterial hypertension [20].

COX is another major ROS source in hypertensive disease. Indeed, COX metabolises arachidonic acid from membrane-bound phospholipids into a final variety of bioactive prostaglandins and thromboxane (TX) A_2, collectively termed prostanoids [21]. Prostacyclin is the major prostanoid released by endothelial cells mediating several protective effects on the vascular wall [22]. Its predominant opponent is TXA_2, specifically acting on thromboxane–prostanoid receptors mainly located on smooth muscle cells where it causes vasoconstriction [23]. Two distinct COX isoenzymes, COX-1 and COX-2, have been described. While COX-1 is constitutively expressed to produce physiologically relevant prostanoids, COX-2 is regarded as an inducible isoform, which can be rapidly upregulated by a number of stimuli. In isolated small resistance arteries from essential hypertensive patients it was recently found an overexpression and increased activity of COX-2 occur, playing a major role in reducing NO availability. When incubated with a selective COX-2 inhibitor, the intravascular $\bullet O_2^-$ excess was strongly reduced, thus demonstrating COX-2 as a major ROS source in hypertension [24].

A role for mitochondrial dysfunction and excessive ROS production in the development of arterial hypertension has been repeatedly suggested. Mitochondrial abnormalities including mitochondrial dwelling, decreased mitochondrial mass and density are observed in hypertension and result in impaired energy production and accelerated formation of ROS through instability of the mitochondrial respiratory chain [25].

The profound increase of hypertension with age is associated with the decline of the NAD^+ dependent deacetylase activity of Sirt3 which is accompanied by a reduced mitochondrial energy metabolism and increased mitochondrial ROS production [26]. SIRT3 is a metabolic sensor that uses intracellular metabolites such as NAD^+ and acetyl-CoA to modulate mitochondrial function to match nutrient supply [27]. It activates mitochondrial superoxide dismutase 2 (SOD2) resulting in a potent mitochondrial antioxidant activity that is progressively lost with ageing as its expression declines by 40% by age 65. Importantly, these molecular alterations parallel the increased incidence of hypertension with ageing [28].

Beyond its influence on the peripheral vascular system, increasing evidence suggests that mitochondria-derived ROS play an important role also in the central regulation of systemic cardiovascular function [29]. Recent data suggest that activation of the renin-angiotensin system in the brain stimulates intraneuronal signalling, that leads to an increased $\bullet O_2^-$ generation [29], ultimately resulting in a modulation of the neuronal membrane potential by activation of specific ion channels and increased neuronal firing [30]. These alterations are thought to play a key role in the central regulation of blood pressure.

4. Role of angiotensin II on vascular ROS generation

Ang II represents one of the major vasoactive peptides involved in the regulation and activation of NAD(P)H oxidase, together with cytokines and growth factors. Ang II, via AT1 receptors, stimulates activation of NAD(P)H oxidase, increases expression of NAD(P)H oxidase subunits, and induces vascular ROS generation [13]. Of note, ROS may regulate AT1 receptor gene expression, which in turn modulates ROS generation, thus creating a vicious circle [31]. The strict cross-talk between Ang II and NAD(P)H oxidase is confirmed by in vivo studies. Thus, in Ang II-infused hypertensive rats, NAD(P)H oxidase subunit expression and activity are increased, and administration of a NAD(P)H oxidase inhibitor reduces vascular $\bullet O_2^-$ generation [32]. Chronic administration of apocynin, a selective inhibitor of NAD(P)H oxidase, prevents vascular remodelling, endothelial dysfunction and collagen deposition at the level of mesenteric resistance arteries from Ang II-infused mice [33]. These data suggest that activation of vascular NAD (P)H oxidase plays an important role in vascular functional and structural changes that accompany the development of hypertension in Ang II-infused mice.

Moreover, apocynin was also able to attenuate the systolic blood pressure rise induced by Ang II [33] (Fig. 1), demonstrating that NAD (P)H oxidase inhibition leads to blood pressure reduction in an Ang II-dependent hypertensive murine model and supporting the concept that NAD(P)H oxidase-derived $\bullet O_2^-$ plays a role in the Ang II-induced blood pressure elevation. These findings are supported by other reports assessing the role for the endogenous RAS in increasing ROS production during hypertension. In the 2-kidney 1-clip model of renovascular hypertension (a model characterised by a high activation of the RAS), endothelial dysfunction was associated with a NAD(P)H oxidase-derived increase of $\bullet O_2^-$ production, a condition which in part participates to blood pressure elevation [34]. In salt-sensitive Dahl rats, another animal model of hypertension characterised by activation of the local RAS, chronic administration with an Ang II receptor blocker dramatically reduced vascular $\bullet O_2^-$ production [35]. Importantly, in animal model of salt-sensitive hypertension, treatment with a gp91phox-containing NAD(P)H oxidase inhibitor also prevented the increased vascular $\bullet O_2^-$ production together with the expression of pro-inflammatory molecules, thus supporting the concept of a linkage between RAS, NAD (P)H oxidase activity, and vascular inflammation [36].

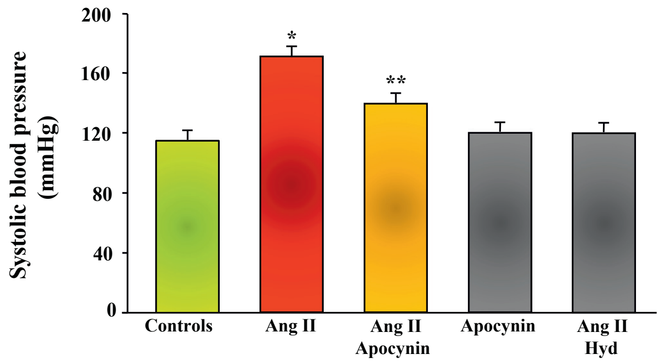

Fig. 1. Systolic blood pressure behavior in Controls and in Angiotensin (Ang) II-infused mice chronically treated or not with Apocynin or Hydralazine (Hyd). It is evident that Apocynin was able to attenuate in part the Ang II-mediated blood pressure elevation. * $P < 0.01$ vs other groups; ** $P < 0.01$ vs Controls, Apocynin and Ang II + Hyd. Adapted from ref. 33.

There is increasing evidence that angiotensin II signals might be mediated, at least in part, by mitochondria-derived production of ROS [37]. Supplementation of MitoTEMPO (a mitochondria-targeted SOD2 mimetic) enhances scavenging of mitochondrial $\bullet O_2^-$ and protects from mitochondrial-derived $\bullet O_2^-$ overproduction. In angiotensin II and DOCA-salt models of hypertension mitoTEMPO supplementation attenuates endothelial oxidative stress, restores NO• production, improves endothelium-dependent vasodilatation and reduces blood pressure [37]. Supplementation of mitoEbselen, another scavenger of mitochondrial ROS that specifically targets H_2O_2 diminished vascular oxidative stress and significantly reduced blood pressure in angiotensin II-induced hypertensive mice [38].

5. Angiotensin II and ROS. Is there a role for the sympathetic nervous system?

Among multiple mechanisms involved in controlling blood pressure homeostasis, a critical role is played by the SNS. After the pioneering evidence of an elevated cardiac output documented in young hypertensive patients, it is now accepted that autonomic dysfunction is a key mechanism accounting for the development of hypertension. In particular, the involvement of the central nervous system as a trigger of an elevated sympathetic outflow is documented [39].

Experimental studies evidenced that the RAS, and in particular the effector peptide Ang II with its AT1 receptors, is overactivated in the brains of SHR [40]. The activation of AT1 receptors at the level of rostral ventrolateral medulla of SHR increases neuronal firing frequency [41]. In line with these observations, it is described that Ang II administration leads to a selective increment in sympathetic tone in high-salt hypertensive rats [9]. The potentiation of RAS activity in brainstems of SHR was further confirmed when AT1 receptor stimulation produced a greater activation of downstream signalling pathways in brainstem cells from SHRs compared with controls [42]. The hypothalamic paraventricular nucleus (PVN) is another central cardiovascular regulatory region which has been shown to mediate sympathetic activity [43]. Inhibition of AT1 receptor in the PVN region from SHR resulted in a significant reduction of peripheral blood pressure, demonstrating a crucial role played by PVN in sympathetic overactivity in this genetic animal model of hypertensive disease [44]. In such a scenario, a crucial role seems to be also played by ROS. This is because the activation of NAD(P)H oxidase via the AT1 receptor activation is considered a major downstream target of Ang II in the brainstem. In particular, it was documented that an increased ROS is a primary mechanism whereby Ang II causes an increased SNS activity [45]. These mechanisms of central regulation of the blood pressure by hyperactivation of the sympathetic activity are further complicated by the contribution of the adaptive immune response and, in particular, T lymphocytes. Sympathetic nerve terminals activate both the T cells in lymph nodes and the expression of homing signals in the vasculature and kidney, promoting the attraction of T cells to these organs. In turn, T cells release cytokines that stimulate the vessel and kidney NADPH oxidases, promoting vasoconstriction and overt hypertension [46] (Fig. 2). In the present issue of the Vascular of Pharmacology, Vieira-Rocha et al. [47] investigate another interplay between SNS and RAS, represented by a fetal exposure to RAS overactivity leading to a future increase in vascular responsiveness and hypertension after delivery. Demonstration that poor fetal growth contributes to the development of hypertension in adult life and the activated RAS is one of the proposed mechanisms represent a crucial background to their working hypothesis [48]. To this aim, the authors utilised adult Sprague-Dawley rats offspring from mothers fed ad-libitum (control) or with 50% intake during the second half of gestation (maternal undernutrition). Sympathetic neurotransmission was studied in mesenteric/tail arteries and mesenteric veins. The novel aspect of this study is the demonstration that AT1R inhibition by losartan induced a vascular tonic facilitation only in offspring from under-nutrited mothers. These findings were supported

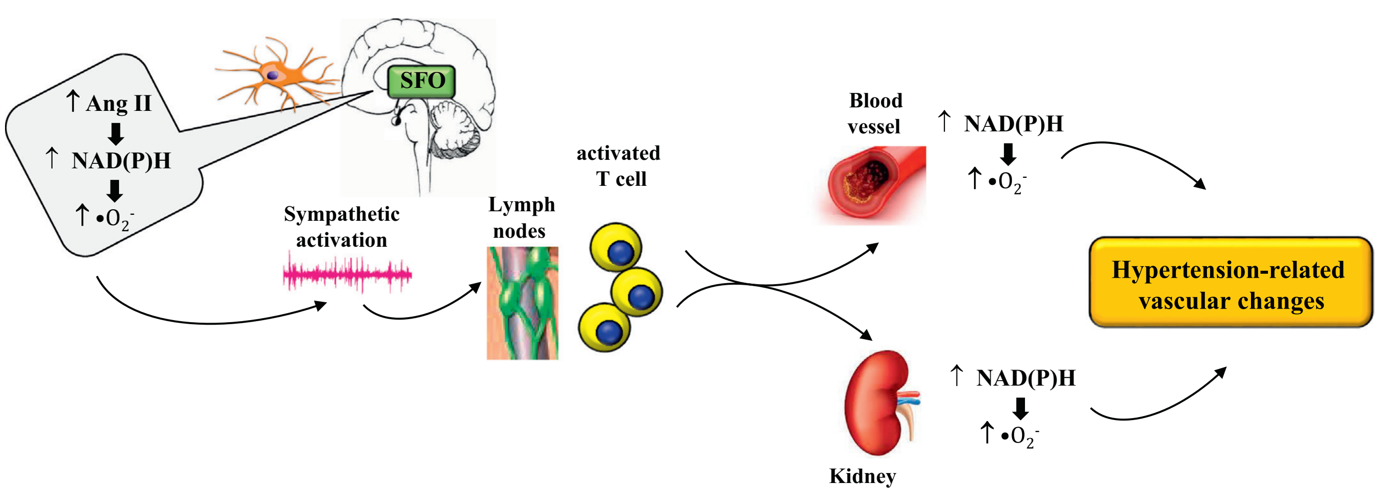

Fig. 2. Proposed cross-talk between cerebral and peripheral oxidative stress and sympathetic nervous system activation in the pathogenesis of hypertensive-related vascular changes. In this picture, angiotensin (Ang) II stimulates an NADPH oxidase in the subfornical organs (SFO) of the brain, thus stimulating a sympathetic activation. Sympathetic nerve terminals in lymph nodes activate T cells, which in turn stimulate the vascular and kidney generation of NADPH oxidases, promoting the hypertensive-related vascular changes.

by the demonstration that sympathetic vascular innervation and AT1R density were larger in the group from maternal undernutrition compared with controls. The study provides intriguing information that may represent the background for future research in this area. In particular, for the first time in an adult murine model, it is demonstrated that an increased vascular sympathetic activity secondary to an inappropriate RAS activation may play an important role on hypertension development subsequent to fetal undernutrition. Future studies will establish the role of oxidative stress in mediating the abnormal and early interplay between RAS and SNS.

6. Conclusions

ROS are generated within the vascular wall, at the level of endothelial and vascular smooth muscle cells. Under pathological conditions, the ROS generation exceeds the usual protective antioxidant mechanisms, leading to a state of oxidative stress. Hypertension is characterised by a high generation of ROS. While in the past a major source of vascular ROS detected in hypertension was considered the hyperactivity of the NAD(P)H oxidase, increasing evidence suggests that also mitochondria dysfunction might significantly contribute to the burden of vascular ROS. Ang II represents the major vasoactive peptide derived by a RAS activation which is involved in the stimulation of NAD(P)H oxidase and might also influence the production of mitochondrial ROS. In such a scenario, it was also demonstrated the crucial role played by a potentiation of cerebral RAS activity which, in turn, was able to trigger several downstream signalling pathways which may stimulate the SNS activity. An excess of the NAD(P)H oxidase is considered a major downstream target of Ang II in the brainstem. More recently, it was proposed that stress factors during fetal life, particularly undernutrition, might contribute to the development of adult hypertension, throughout mechanisms that involve vascular SNS hyperactivation and tonic facilitation of prejunctional AT1 receptors by endogenous Ang II. Future research hopefully will clarify the role, if any, of ROS excess in this strict relationship between RAS and SNS overactivity which characterises fetal stress condition.

References

[1] A. Virdis, C. Savoia, G. Grassi, G. Lembo, C. Vecchione, G. Seravalle, et al., Evaluation of microvascular structure in humans: a 'state-of-the-art' document of the Working Group on Macrovascular and Microvascular Alterations of the Italian Society of Arterial Hypertension, J. Hypertens. 32 (11) (2014) 2120–2129.
[2] H.D. Intengan, E.L. Schiffrin, Structure and mechanical properties of resistance arteries in hypertension: role of adhesion molecules and extracellular matrix determinants, Hypertension 36 (3) (2000) 312–318.
[3] M.F. Neves, A. Virdis, E.L. Schiffrin, Resistance artery mechanics and composition in angiotensin II-infused rats: effects of aldosterone antagonism, J. Hypertens. 21 (1) (2003) 189–198.
[4] R.M. Bruno, E. Duranti, C. Ippolito, C. Segnani, N. Bernardini, G. Di Candio, et al., Different Impact of Essential Hypertension on Structural and Functional Age-Related Vascular changes, Hypertension 69 (1) (2017) 71–78.
[5] A. Virdis, M.F. Neves, F. Amiri, E. Viel, R.M. Touyz, E.L. Schiffrin, Spironolactone improves angiotensin-induced vascular changes and oxidative stress, Hypertension 40 (4) (2002) 504–510.
[6] A. Virdis, R. Colucci, M. Fornai, E. Duranti, C. Giannarelli, N. Bernardini, et al., Cyclooxygenase-1 is involved in endothelial dysfunction of mesenteric small arteries from angiotensin II-infused mice, Hypertension 49 (3) (2007) 679–686.
[7] A. Warnholtz, G. Nickenig, E. Schulz, R. Macharzina, J.H. Brasen, M. Skatchkov, et al., Increased NADH-oxidase-mediated superoxide production in the early stages of atherosclerosis: evidence for involvement of the renin-angiotensin system, Circulation 99 (15) (1999) 2027–2033.
[8] R. Touyz, S. EL, Signal transduction mechanisms mediating the physiological and pathophysiological actions of angiotensin II in vascular smooth muscle cells, Pharmacol. Rev. 52 (2000) 639–672.
[9] J.W. Osborn, G.D. Fink, Region-specific changes in sympathetic nerve activity in angiotensin II-salt hypertension in the rat, Exp. Physiol. 95 (1) (2010) 61–68.
[10] K.K. Griendling, D. Sorescu, B. Lassegue, M. Ushio-Fukai, Modulation of protein kinase activity and gene expression by reactive oxygen species and their role in vascular physiology and pathophysiology, Arterioscler. Thromb. Vasc. Biol. 20 (10) (2000) 2175–2183.
[11] U. Landmesser, D.G. Harrison, Oxidative stress and vascular damage in hypertension, Coron. Artery Dis. 12 (6) (2001) 455–461.
[12] R.M. Touyz, E.L. Schiffrin, Ang II-stimulated superoxide production is mediated via phospholipase D in human vascular smooth muscle cells, Hypertension 34 (4 Pt 2) (1999) 976–982.
[13] R.M. Touyz, F. Tabet, E.L. Schiffrin, Redox-dependent signalling by angiotensin II and vascular remodelling in hypertension, Clin. Exp. Pharmacol. Physiol. 30 (11) (2003) 860–866.
[14] R.M. Touyz, E.L. Schiffrin, Reactive oxygen species in vascular biology: implications in hypertension, Histochem. Cell Biol. 122 (4) (2004) 339–352.
[15] T.M. Paravicini, R.M. Touyz, Redox signaling in hypertension, Cardiovasc. Res. 71 (2) (2006) 247–258.
[16] H. Suzuki, F.A. DeLano, D.A. Parks, N. Jamshidi, D.N. Granger, H. Ishii, et al., Xanthine oxidase activity associated with arterial blood pressure in spontaneously hypertensive rats, Proc. Natl. Acad. Sci. U. S. A. 95 (8) (1998) 4754–4759.
[17] S. Masi, R. Colucci, E. Duranti, M. Nannipieri, M. Anselmino, C. Ippolito, et al., Aging Modulates the Influence of Arginase on Endothelial Dysfunction in Obesity, Arterioscler. Thromb. Vasc. Biol. 38 (10) (2018) 2474–2483.
[18] U. Landmesser, S. Dikalov, S.R. Price, L. McCann, T. Fukai, S.M. Holland, et al., Oxidation of tetrahydrobiopterin leads to uncoupling of endothelial cell nitric oxide synthase in hypertension, J. Clin. Invest. 111 (8) (2003) 1201–1209.
[19] Y. Higashi, S. Sasaki, K. Nakagawa, Y. Fukuda, H. Matsuura, T. Oshima, et al., Tetrahydrobiopterin enhances forearm vascular response to acetylcholine in both normotensive and hypertensive individuals, Am. J. Hypertens. 15 (4 Pt 1) (2002) 326–332.
[20] A. Virdis, E. Duranti, R. Colucci, C. Ippolito, E. Tirotta, G. Lorenzini, et al., Ghrelin restores nitric oxide availability in resistance circulation of essential hypertensive patients: role of NAD(P)H oxidase, Eur. Heart J. 36 (43) (2015) 3023–3030.
[21] F. Cipollone, B. Rocca, C. Patrono, Cyclooxygenase-2 expression and inhibition in atherothrombosis, Arterioscler. Thromb. Vasc. Biol. 24 (2) (2004) 246–255.
[22] C.D. Funk, Prostaglandins and leukotrienes: advances in eicosanoid biology, Science 294 (5548) (2001) 1871–1875.
[23] D. Yang, M. Feletou, N. Levens, J.N. Zhang, P.M. Vanhoutte, A diffusible substance(s) mediates endothelium-dependent contractions in the aorta of SHR, Hypertension 41 (1) (2003) 143–148.
[24] A. Virdis, A. Bacca, R. Colucci, E. Duranti, M. Fornai, G. Materazzi, et al., Endothelial dysfunction in small arteries of essential hypertensive patients: role of cyclooxygenase-2 in oxidative stress generation, Hypertension 62 (2) (2013) 337–344.
[25] R.M. Touyz, Reactive oxygen species, vascular oxidative stress, and redox signaling in hypertension: what is the clinical significance? Hypertension 44 (3) (2004) 248–252.
[26] R.H. Houtkooper, J. Auwerx, Exploring the therapeutic space around NAD+, J. Cell Biol. 199 (2) (2012) 205–209.
[27] M.D. Hirschey, T. Shimazu, J.Y. Huang, E. Verdin, Acetylation of mitochondrial proteins, Methods Enzymol. 457 (2009) 137–147.
[28] K.N. Chaudhry, P. Chavez, J. Gasowski, T. Grodzicki, F.H. Messerli, Hypertension in the elderly: some practical considerations, Cleve. Clin. J. Med. 79 (10) (2012) 694–704.
[29] A.J. Case, S. Li, U. Basu, J. Tian, M.C. Zimmerman, Mitochondrial-localized NADPH oxidase 4 is a source of superoxide in angiotensin II-stimulated neurons, Am. J. Physiol. Heart Circ. Physiol. 305 (1) (2013) H19–H28.
[30] J.X. Yin, R.F. Yang, S. Li, A.O. Renshaw, Y.L. Li, H.D. Schultz, et al., Mitochondria-produced superoxide mediates angiotensin II-induced inhibition of neuronal potassium current, Am. J. Phys. Cell Physiol. 298 (4) (2010) C857–C865.
[31] G. Nickenig, K. Strehlow, A.T. Baumer, S. Baudler, S. Wassmann, H. Sauer, et al., Negative feedback regulation of reactive oxygen species on AT1 receptor gene expression, Br. J. Pharmacol. 131 (4) (2000) 795–803.
[32] F.E. Rey, M.E. Cifuentes, A. Kiarash, M.T. Quinn, P.J. Pagano, Novel competitive inhibitor of NAD(P)H oxidase assembly attenuates vascular O(2)(−) and systolic blood pressure in mice, Circ. Res. 89 (5) (2001) 408–414.
[33] A. Virdis, M.F. Neves, F. Amiri, R.M. Touyz, E.L. Schiffrin, Role of NAD(P)H oxidase on vascular alterations in angiotensin II-infused mice, J. Hypertens. 22 (3) (2004) 535–542.
[34] O. Jung, J.G. Schreiber, H. Geiger, T. Pedrazzini, R. Busse, R.P. Brandes, gp91phox-containing NADPH oxidase mediates endothelial dysfunction in renovascular hypertension, Circulation 109 (14) (2004) 1795–1801.
[35] M.S. Zhou, A.G. Adam, E.A. Jaimes, L. Raij, In salt-sensitive hypertension, increased superoxide production is linked to functional upregulation of angiotensin II, Hypertension 42 (5) (2003) 945–951.
[36] M.S. Zhou, I. Hernandez Schulman, P.J. Pagano, E.A. Jaimes, L. Raij, Reduced NAD(P)H oxidase in low renin hypertension: link among angiotensin II, atherogenesis, and blood pressure, Hypertension 47 (1) (2006) 81–86.
[37] A.E. Dikalova, A.T. Bikineyeva, K. Budzyn, R.R. Nazarewicz, L. McCann, W. Lewis, et al., Therapeutic targeting of mitochondrial superoxide in hypertension, Circ. Res. 107 (1) (2010) 106–116.
[38] S.I. Dikalov, R.R. Nazarewicz, A. Bikineyeva, L. Hilenski, B. Lassegue, K.K. Griendling, et al., Nox2-induced production of mitochondrial superoxide in angiotensin II-mediated endothelial oxidative stress and hypertension, Antioxid. Redox Signal. 20 (2) (2014) 281–294.
[39] D. Haspula, M.A. Clark, Neuroinflammation and sympathetic overactivity: Mechanisms and implications in hypertension, Auton. Neurosci. 210 (2018) 10–17.
[40] S.J. Veerasingham, M.K. Raizada, Brain renin-angiotensin system dysfunction in hypertension: recent advances and perspectives, Br. J. Pharmacol. 139 (2) (2003) 191–202.
[41] T. Matsuura, H. Kumagai, A. Kawai, H. Onimaru, M. Imai, N. Oshima, et al., Rostral ventrolateral medulla neurons of neonatal Wistar-Kyoto and spontaneously hypertensive rats, Hypertension 40 (4) (2002) 560–565.
[42] S. Negussie, A. Lymperopoulos, M.A. Clark, Role of betaarrestin1 in AT1 R-

mediated MAPK activation in Wistar and SHR brainstem astrocytes, J. Neurochem. 148 (1) (2018) 46–62.

[43] R.A. Dampney, M. Fontes, Y. Hirooka, J. Horiuchi, P.D. Potts, T. Tagawa, Role of angiotensin II receptors in the regulation of vasomotor neurons in the ventrolateral medulla, Clin. Exp. Pharmacol. Physiol. 29 (5–6) (2002) 467–472.

[44] Z. Shan, J. Zubcevic, P. Shi, J.Y. Jun, Y. Dong, T.M. Murca, et al., Chronic knockdown of the nucleus of the solitary tract AT1 receptors increases blood inflammatory-endothelial progenitor cell ratio and exacerbates hypertension in the spontaneously hypertensive rat, Hypertension 61 (6) (2013) 1328–1333.

[45] T. Kishi, Y. Hirooka, Oxidative stress in the brain causes hypertension via sympathoexcitation, Front. Physiol. 3 (2012) 335.

[46] D.G. Harrison, M.C. Gongora, Oxidative stress and hypertension, Med. Clin. North Am. 93 (3) (2009) 621–635.

[47] M.S. Vieira-Rocha, P. Rodriguez-Rodriguez, J.B. Sousa, M.C. Gonzales, S.M. Arribas, A.L. Lopez de Pablo, et al., Vascular Angiotensin AT1 receptor neuromodulation in fetal programming of hypertension, Vasc. Pharmacol. (2018) (XXXXXXX).

[48] A.C. Marshall, H.A. Shaltout, N.T. Pirro, J.C. Rose, D.I. Diz, M.C. Chappell, Enhanced activity of an angiotensin-(1-7) neuropeptidase in glucocorticoid-induced fetal programming, Peptides 52 (2014) 74–81.