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Reactive Oxygen Species and Cardiovascular Diseases

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1. Introduction

Reduction or oxidation caused by addition or loss of any electron is responsible for alterations in functional and structural profile of molecules, hence, changing signaling mechanism. Reactive free radicals play a crucial role in different physiological mechanisms ranging from the immune defense to cell signaling and inflammation (Elahi & Matata, 2006). There is increasing evidence that irregular production of free radicals lead to enhanced stress on cellular structures and causes changes in molecular pathways that underpins the pathogenesis of several relevant human disorders, such as cancer, heart diseases, the process of physiological ageing and neurological diseases (Pacher & Szabo, 2008; Lushchak, 2011a; Lushchak, 2011b). Comprehending the involvement of free radical stress in the pathogenesis of disease will allow us to investigate the development of oxidative stress; a condition that occurs due to an imbalance between cellular production of oxidant molecules and the availability of appropriate antioxidants species that defend against them. It is hoped that this knowledge will subsequently lead to the development of effective therapeutic interventions against oxidative stress.

The main molecules that are involved in redox signaling are called as reactive oxygen species (ROS), in which we may include hydrogen peroxide (H_2O_2), nitric oxide (NO), hydroxyl radical, superoxide ($O^{2\bullet-}$) and peroxynitrite. Current redox signaling investigations indicate that all the vascular constituents, including vascular smooth muscle cells (VSMCs), endothelial and adventitial cells and macrophages, produce ROS (Papaharalambus & Griendling, 2007). ROS are involved in signal transduction which is related to relaxation and contraction of blood vessels, migration, growth and death of vascular cells, and also extracellular matrix (ECM) alterations.

It is known that vascular diseases such as peripheral vascular disease, coronary artery disease and cerebrovascular diseases are the largest cause of morbidity and mortality in industrialized countries. Some common risk factors for vascular disease, including diabetes and hypertension are still prevalent in Western and other populations, indicating that vascular disease will possible continue to impose a substantial burden on health care resources throughout the next generation. The earliest detectable changes in vascular

disease states are irregularities of the endothelium, resulting in loss of the endothelium's normal homeostatic functions that normally act to inhibit disease-related mechanisms such as thrombosis and inflammation. Particularly, it was previously demonstrated that nitric oxide (NO) produced by NO synthase (eNOS) in the vascular endothelium modulates blood flow and pressure and presents important antiatherogenic effects on platelets, vascular smooth muscle and endothelial cells (Umans and Levi, 1995).

Many previous studies have already demonstrated the effects of oxidative stress on the cardiovascular system. Superoxide dismutase (SOD), an enzyme that catalyze the dismutation of $O^{2\bullet-}$ into oxygen and H_2O_2, injected into brainstem areas involved in cardiovascular regulation decreased sympathetic nerve activity and decreased blood pressure in swine (Zanzinger and Czachurski, 2009). According to Campese et al. (2004) the lack of low-density lipoprotein (LDL) receptor-enhanced cholesterol blood levels enhanced ROS and impared baroceptor reflex function. Monahan et al (2004) indicated that oxidative stress collaborates to age-associated decreases in cardiovagal baroreflex sensitivity in healthy subjects. Conversely, it was indicated in male smokers that circulating antioxidants had no effect on baroceptor reflex, and minor effects on the cardiovascular system were seen following acute fat and vitamin ingestion (Wright et al, 2009). Overall, comprehending the process which redox signaling modulates cardiovascular system will provide further precise ROS regulation as a therapy for cardiovascular disorders. In this chapter we summarize concepts regarding oxidative stress related to cardiovascular disorders.

2. Models of ROS-induced cardiovascular diseases

Basic science applied in animal is indispensable to comprehend the pathogenesis, mechanisms involved in therapeutic agents, molecular process, and environmental or genetic factors that increases the risks of disease development. The species of animal studied are influenced by numerous aspects. Usually, animals with small size are preferred because they are more manageable and experiments are less expensive. According to the guide of the principles of animal research, we should use the lowest possible animal and, nowadays, permission would not be granted for using larger animals unless a similar experiment could not be performed on rodent. Nevertheless, a major criticism of using rodents is that they may not adequately correspond to the human situation and this fact occasionally justifies the use of larger animals such as pigs and monkeys (Rees & Alcolado, 2005). In this topic we described the main animal models used in the literature to investigate the mechanisms involved in ROS-induced cardiovascular disorders.

The relationship between enhanced ROS and hypertension is well established in many studies involving diet or endocrine-induced and surgically-induced hypertensive animals (Banday et al, 2007). A variety of evidence suggests that ROS collaborate to impaired endothelial function in several forms of hypertension and that there is enhanced ROS in the microvessels of spontaneously hypertensive rats (SHR) and Dahl salt-sensitive hypertensive rats (Manning et al, 2003). An interesting study by Lenda et al (2000) suggested that ROS can also collaborate to a decreased endothelium-dependent dilation in normotensive rats under an enhanced salt diet. Although the latent level of ROS in contributing to damaged endothelium-dependent vasodilation and decreased NO production during increased dietary salt intake, the nature and mechanisms of the impaired vascular relaxation with the

high-salt diet and the role of enhanced ROS in contributing to salt-induced changes in vascular function and hypertension are not completely understood (Cai & Harrison, 2000).

Hypertension is a result of enhanced ROS, however, data regarding the most potent cause of ROS-induced hypertension is controversial. In fact, oxidative stress does not elucidate the cause of every kind of hypertension, which develops through many processes. A small number of clinical investigations indicated the protective property of antioxidants (Ceriello et al, 1991; Galley et al, 1997). Nevertheless, it is known that not all animal models of hypertension are related to ROS (Rajagopalan et al, 1996). Additionally, clinical studies demonstrated negative correlation between arterial pressure and oxidative stress markers in subjects with mild to moderate hypertension (Cracowski et al, 2003). It is hard to find a cause–effect association between hypertension and oxidative stress in clinical studies, however, some studies indicated that increased ROS is a risk factor for human hypertension (Adbilla et al, 2007).

Animal models are important to support the link between hypertension and oxidative stress. Some procedures performed in animal models helped to comprehend the mechanisms involved in ROS-induced hypertension (Rajagopalan et al, 1996; Puzserova et al, 2010; Valenti et al, 2011a).

The group of Zucker and coworkers from Nebraska have used a model based on heart failure in rabbits (Mousa et al, 2008). According to their method, a platinum wire pacing electrode is sutured to the epicardium of the left ventricle in the rabbits. A ground electrode is secured to the left atrium. All wires are tunneled beneath the skin and exited in the midscapular area. The chest is closed and evacuated; in the same setting, a radiotelemetry unit is implanted into the right femoral artery with the tip of its catheter in the descending aorta to monitor blood pressure and heart rate in the conscious state. Rabbits were allowed to recover from surgery for two weeks before they were used in the study. They developed a rapid pacing model of chronic heart failure. After recovery from surgery, animals are paced at a rate of 360–380 beats/min with the use of a small, light-weight pacing unit of their own design. The pacing rate is adjusted and monitored by frequent echocardiograms. In general, each rabbit is paced at 360 beats/minute for the first week to determine whether it would tolerate this protocol. After the first week, the pacing rate is enhanced to 380 beats/minute and continued at this rate for the remainder of the protocol. The rabbits are continuously paced for 3 weeks. Cardiac dimensions (left ventricular end-diastolic diameter, left ventricular end-systolic diameter, fractional shortening, and ejection fraction) and other hemodynamic parameters are monitored on a weekly basis. Additionally, to left ventricular dimension changes, clinical signs of chronic heart failure such as ascites, pulmonary congestion, and cachexia are appreciated as symptoms of this chronic heart failure model. This model is well accepted in the literature and it was observed enhanced production of ROS in the heart and in the brainstem. Furthermore, they measured two of the three major SOD isoforms (Cu,Zn-SOD and Mn-SOD) and the catalytic subunit of NAD(P)H oxidase, gp91phox into the brainstem. They reported that protein expression of both CuZn SOD and Mn SOD was significantly downregulated in the chronic heart failure condition. The gp91phox protein was significantly enhanced in chronic heart failure rabbits (Gao et al, 2007). The more affected area was the rostroventrolateral area of the medulla oblongata.

The renovascular model of hypertension is a model which presented enhanced level of ROS (Campos et al, 2011). In this model, rats are anesthetized with ketamine and xylazine (40 mg and 10 mg/kg, respectively, ip); the left renal artery is exposed through an abdominal incision, and the renal artery and renal vein are dissected free from the adherent tissues. The left renal artery is partially obstructed with a silver clip of 0.2-mm width. No clip obstruction is applied to the sham-operated group (n = 15). Animals are submitted to the final experimental procedures 3 or 6 weeks after the surgical procedure. Systolic blood pressure is measured in conscious rats using a pneumatic tail-cuff method.

The role of ROS has been shown in this model of ROS-induced cardiovascular injury, in which the chronic administration of a SOD mimetic, tempol, to reduce ROS was shown to reduce blood pressure (Welch et al, 2003). Moreover, tempol was more effective than AT1 antagonist (candesartan) in reducing blood pressure and in improving renal function in renovascular hypertensive rats, suggesting that ROS plays an important role in mediating of renovascular hypertension (Palm et al, 2010). However, besides the actions of ROS on many tissues, the brain is one of the Ang II targets most affected by ROS. Even when an increase in plasma renin activity is modest after moderate renal artery stenosis, ROS remains increased and collaborates to hypertension (Lerman et al, 1991).Therefore, the involvement of Ang II is believed to decline, whereas ROS increases, during the progression of the 2K1C model. Our hypothesis is that even with a modest increase in circulating Ang II, this peptide acting in the CNS through AT1 receptors might collaborate to NADPH activation, which leads to an increase in local ROS production, causing sympathoexcitation and arterial hypertension.

The central regulation of the sympathetic nervous system (SNS) involved in cardiovascular regulation is complex, involving multiple reflex pathways and neural connections with a large number of neurotransmitters and neuromodulators acting in specific groups of neurons in the CNS involved in the tonic and reflex control of the cardiovascular system. In the CNS, Ang II is able to increase sympathetic vasomotor tone and blood pressure, and is involved in the pathogenesis of many experimental models of hypertension (Campos, 2009). Therefore, the close functional association between NADPH oxidase and the Ang II is of particular relevance in linking oxidative stress in the brain to sympathoexcitation and hypertension. For instance, intracerebroventricular infusion of NADPH oxidase inhibitor antagonizes the pressor response induced by centrally mediated Ang II actions (Gao et al, 2007). In the brain, the overexpression of SOD, an enzyme responsible for $O^{2\bullet-}$ breakdown, also abolishes the central pressor effect of the octapeptide, suggesting that in the CNS there is a positive correlation between the increase in ROS and the central pressor response mediated by Ang II (Zimmerman et al, 2004). Considering that the paraventricular nucleus of the hypothalamus (PVN) and the rostroventrolateral medulla (RVLM) contain critically important neurons involved in the control of sympathetic vasomotor tone and arterial pressure (Valenti et al, 2011a), in the studies reviewed in this article it was examined an increase in AT1 receptor expression and oxidative stress markers within these two nuclei in renovascular hypertension. NAD(P)H oxidase subunits (p47phox and gp91phox) and anti-oxidant enzyme CuZnSOD mRNA expression were quantified in the RVLM and PVN of renovascular hypertensive rats. It was hypothesized that the overactivity of NADPH oxidase-derived ROS associated with a reduction in the activity of CuZnSOD within the RVLM and PVN could collaborate to renovascular hypertension, particularly in the renin-dependent phase of hypertension.

In hypertensive renovascular rats, there is a significant increase in systemic ROS, estimated by the thiobarbituric acid reactive substance (TBARS) level in plasma, compared with control rats. Administration of tempol or Vitamin C systemically decreased blood pressure and RSNA only in renovascular hypertensive rats, indicating that the depressor effect in response to the anti-oxidant administration is mediated by a reduction in sympathetic vasomotor activity (Oliveira-Sales et al, 2008).

Some studies evaluated the effects of ROS on vascular properties in rat aorta (Toba et al, 2010; Olukman et al, 2010). Others tried to reveal the mechanisms involved in ROS-induced cardiovascular disease inside the brainstem (Zanzinger et al, 2009; Valenti et al, 2011a; Campos et al, 2011).

The SHR is a model which has been well investigated (He et al, 2011). SHR and stroke-prone SHR (SPSHR), genetic models that develop hypertension spontaneously, exhibit enhanced NAD(P)H driven $O^{2\bullet-}$ generation in resistance (mesenteric) and conduit (aortic) vessels (Rodriguez-Iturbe et al, 2003). This is associated with NAD(P)H oxidase subunit overexpression and enhanced oxidase activity (Kishi et al, 2004). Several polymorphisms in the promoter region of the p22phox gene have been identified in SHR (Zalba et al, 2001). This has clinical relevance because an association between a p22phox gene polymorphism and NAD(P)H oxidase–mediated $O^{2\bullet-}$ production in the vascular wall of patients with hypertension and atherosclerosis has been described (Moreno et al, 2003).

Enhanced expression of p47phox has been reported in the renal vasculature, macula densa, and distal nephron from young SHR, suggesting that renal NAD(P)H oxidase upregulation precedes development of hypertension (Kishi et al, 2004). Diminished nitric oxide bioavailability as a consequence of enhanced vascular $O^{2\bullet-}$ generation and downregulation of the thioredoxin system may also collaborate to oxidative stress in SHR and SPSHR (Touyz 2003). Treatment with antioxidant vitamins, NAD(P)H oxidase inhibitors, SOD mimetics, and BH_4 and Ang II type-1 (AT1) receptor blockers decrease vascular $O^{2\bullet-}$ production and attenuate development of hypertension in these models (Rodriguez-Iturbe et al, 2003; Shokoji et al, 2003). Taken together, these findings suggest that oxidative stress in genetic hypertension involves enhanced NAD(P)H oxidase activity and dysfunctional endothelial nitric oxide synthase (uncoupled NOS) and is regulated, in part, by AT1 receptors. Figure 1 presents a surgical procedure to record mean arterial pressure and heart rate, while Figure 2 shows recordings from one normotensive Wistar Kyoto and one SHR rat illustrating reflex bradycardia (top) in response to blood pressure increases. In this Figure we may observe the enhanced mean arterial pressure of the SHR compared to the control animal.

In animal models of diabetes, several functional and structural alterations of the heart or in cardiac muscle have been documented (Russel et al, 2006). In most studies of type 1 diabetes mellitus, diabetes are induced after administration of the pancreatic beta-cell toxin streptozotocin, and most studies of type 2 diabetes mellitus have been performed in genetic models of obesity and insulin resistance such as the Zucker fatty rat or db/db mice, both of which have mutations that impair leptin receptor signaling, or ob/ob mice, which lacks leptin. Furthermore, because diabetes mellitus develops at varying tempos in these models, it is important to bear in mind that studies performed in animals before the onset of diabetes may reflect changes that are secondary to the underlying obesity and insulin resistance, and

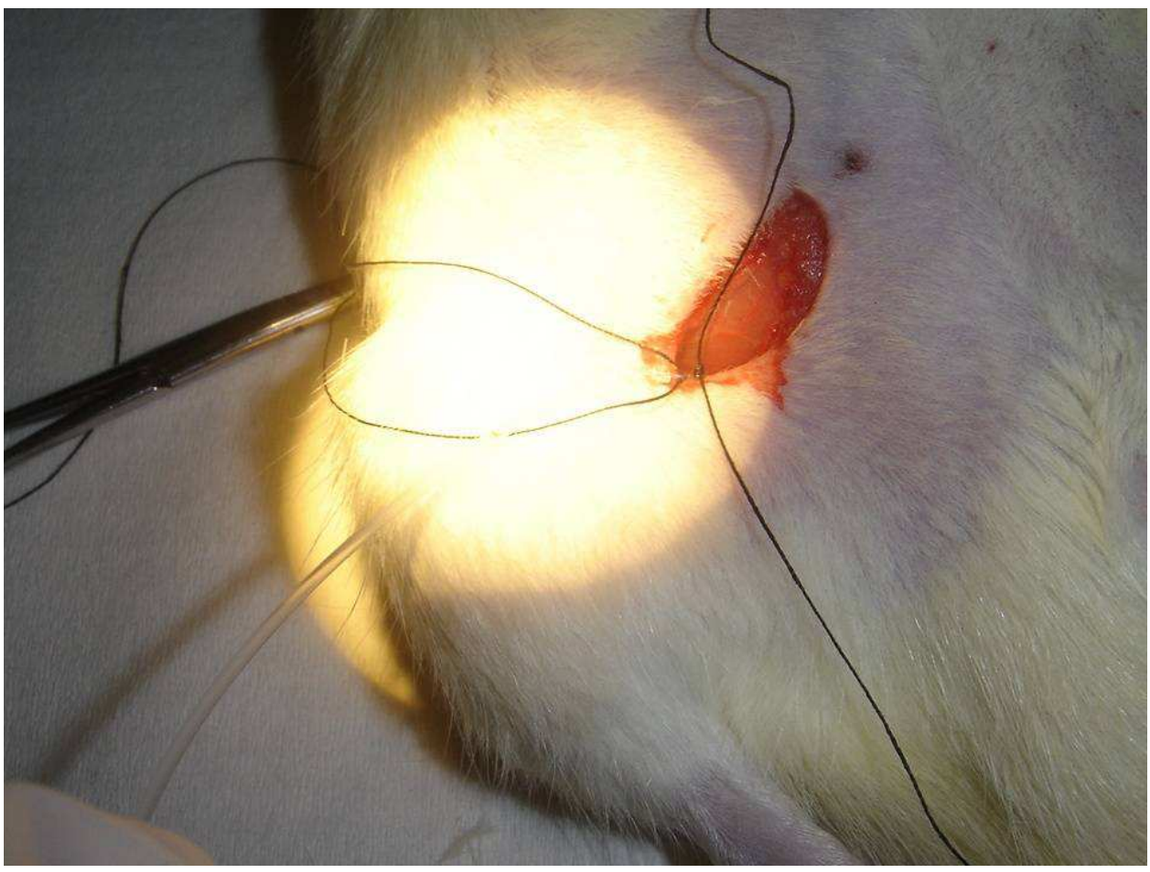

Fig. 1. Surgical procedure to record basal mean arterial pressure and heart rate in one spontaneously hypertensive rat.

studies performed after the onset of diabetes may reflect the added effects of hyperglycemia of various durations. Most studies have been performed in isolated perfused hearts and reveal depressed cardiac function (Aasum et al, 2002; Aasum et al, 2003). In vivo studies in these rodent models have provided evidence for systolic and diastolic dysfunction by echocardiography (Christoffersen et al, 2003) but in some studies using invasive left ventricle catheterization in mouse models of obesity and diabetes mellitus, left ventricle contractility as determined by developed pressure/developed tension was initially enhanced and may reflect the impact of the enhanced plasma volume and perhaps sympathetic activation associated in part with the underlying obesity (Buchanan et al, 2005). These first observations were additionally clarified later (Van den Bergh et al, 2006). It was assessed the hemodynamic changes in db/db mouse hearts in vivo using a pressure–volume instrument. It was reported decreased contractility using load-independent variables such as preload recruitable stroke work, but steady-state measurements of cardiac output and other load-dependent parameters were increased in db/db mice compared with control mice because of favorable loading conditions, specifically enhanced preload and decreased afterload.

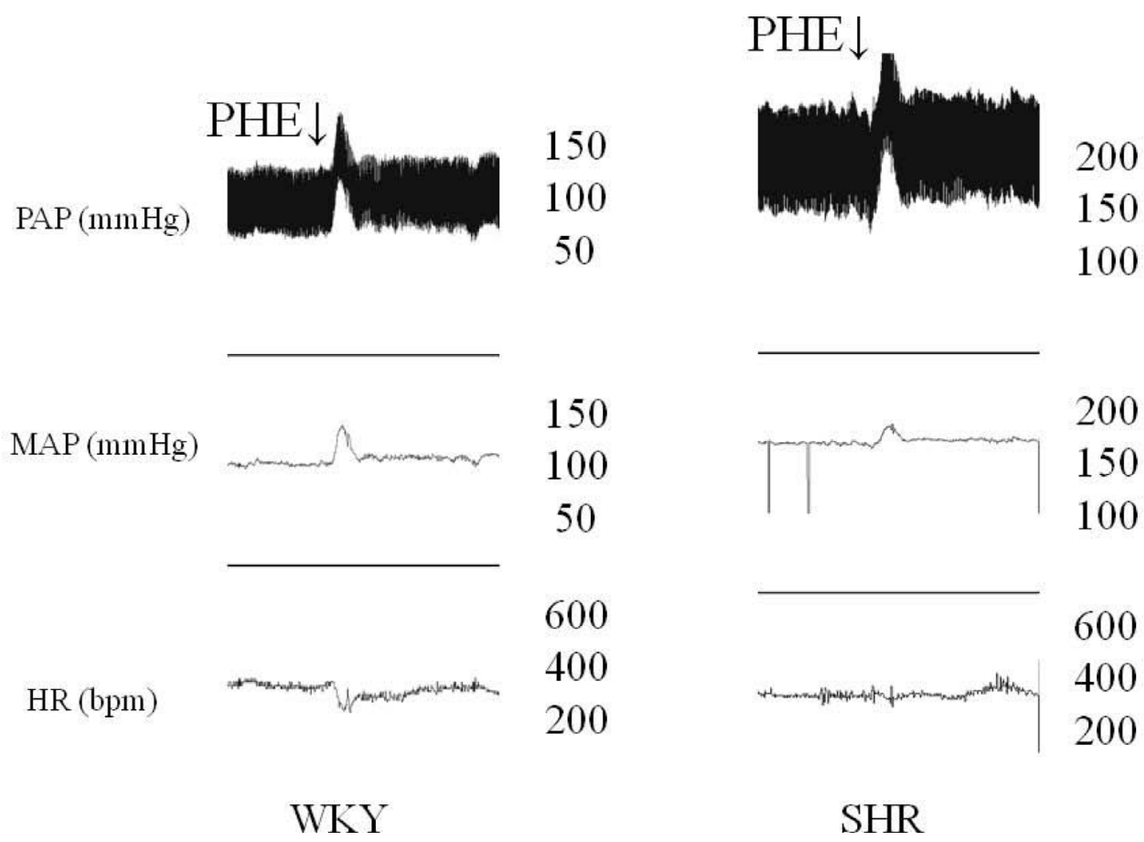

Fig. 2. Recordings from one Wistar Kyoto control rat and one spontaneously hypertensive rat illustrating reflex bradycardia (top) in response to blood pressure increases. Infusions were given in bolus. MAP: mean arterial pressure; PAP: pulsatile arterial pressure; HR: heart rate; PHE: phenylephrine.

Enhanced ROS production in the diabetic heart is a contributing matter to the progression and the development of diabetic cardiomyopathy (Cai et al, 2006). Cumulative superoxide-mediated damage or cellular dysfunction results when an imbalance exists in ROS generation and ROS-degrading pathways. Enhanced ROS generation and impaired antioxidant defenses could both collaborate to oxidative stress in diabetic hearts. Several groups have shown that ROS is overproduced in both type 1 and type 2 diabetes (Cai et al, 2006). Under physiological states, most of the ROS generated within cells arises from mitochondria. Whereas enhanced mitochondrial ROS generation has been shown in various tissues such as endothelial cells that are exposed to hyperglycemia (Brownlee, 1995), relatively few studies to date have directly measured mitochondrial ROS production in mitochondria obtained from diabetic hearts. However, overexpression of mitochondrial superoxide dismutase (SOD2) in the heart of a mouse model of type 1 diabetes mellitus reversed altered mitochondrial morphology and function and maintained cardiomyocyte function (Shen et al, 2006). Evidence also exists for enhanced production of ROS from non mitochondrial sources such as NADPH oxidase or decreased neuronal nitric oxide synthase (NOS1) activity coupled with enhanced activation of xanthine oxidoreductase (Saraiva et al, 2006). Whereas evidence for enhanced ROS production in diabetes mellitus is reasonably

strong, the effect of diabetes on antioxidant defenses in the heart is controversial. Thus, the activities/expression levels of glutathione peroxidase, copper/zinc SOD, or catalase were either enhanced (Li et al, 2006) or decreased (Matkovics et al, 1997). Enhanced ROS generation may activate maladaptive signaling pathways, which may lead to cell death, which could collaborate to the pathogenesis of diabetic cardiomyopathy. Enhanced ROS production was associated with enhanced apoptosis, as evidenced by enhanced in situ nick end-labeling (TUNEL) staining and caspase 3 activation in ob/ob and db/db hearts (Barouch et al, 2003). In the same study, enhanced ROS was also associated with enhanced DNA impairment and loss of activity of DNA repair pathways that declined more rapidly with age in diabetic versus control animals.

Therefore, enhanced ROS-modulated cell death is able to promote irregular cardiac remodeling, which ultimately may collaborate to the morphological characteristic and functional abnormalities that are associated with diabetic cardiomyopathy. In addition to causing cellular injury, enhanced ROS production might lead to cardiac dysfunction via other mechanisms. For instance, enhanced ROS has been proposed to amplify hyperglycemia-induced activation of protein kinase C isoforms, enhanced formation of glucose-derived advanced glycation end products, and enhanced glucose flux through the aldose reductase pathways (Brownlee et al, 1995), which may all collaborate to various ways to the development of cardiac complications in diabetes mellitus. Enhanced ROS also might collaborate to mitochondrial uncoupling, which could impair myocardial energetic metabolism in diabetes.

Strategies that enhance mitochondrial ROS scavenging systems have been demonstrate to be effective in decreasing diabetes-induced cardiac dysfunction. Overexpression of metallothionein, catalase, and manganese SOD (Shen et al, 2006) in the heart reversed diabetic cardiomyopathy in animal models of both type 1 and type 2 diabetes. Therefore, strategies that either reduce ROS or augment myocardial antioxidant defense mechanisms might have therapeutic efficacy in improving myocardial function in diabetes mellitus.

In summary, experimental protocols applied in animals are necessary to understand the pathological events involved in cardiovascular diseases development. However, there are differences between human and animals like rat and mouse. Thus, we should be careful when interpreting data aiming to apply in humans regarding processes related to therapeutic agents, molecular process, and environmental or genetic factors that enhances the risks for cardiovascular disorders development.

3. Sources of ROS in cells

The literature indicated that vascular cells, as well as cardiomyocytes and neurons, produce ROS, contributing to the development of disorders related to the cardiovascular system. Although several enzyme systems produce ROS, many of them are prevalent in pathologic processes. Among the main ROS generators we may include cytochrome P450, the mitochondrial respiratory chain, xanthine oxidase (XO), uncoupled endothelial nitric oxide synthase (eNOS), heme oxygenase, myeloperoxidase, lipoxygenase, cyclooxygenase and NADPH oxidases. Some of these systems have been proven to be relevant to hypertension (Lee & Griendling, 2008).

Others mechanisms involved in ROS production are better described in the chapters from this book. Thus, we will only briefly describe the main sources in this topic.

Based on the literature, the NOX family includes seven members, which are NOX1-5 and DUOX1-2. NOX2 NADPH oxidase is the predominant source of ROS production in humans (Nauseef, 2004). The main sources of ROS are phagocytic cells—neutrophils and macrophages. NOX2-NADPH oxidase is formed by functional transmembrane heterodimers, gp91 phox and p22 phox (also known collectively as the cytochrome b558), and four regulatory cytosolic subunits—p40 phox , p47 phox , p67 phox , and the small GTPase, Rac2. In the dormant state, cytochrome b558 resides in intracellular vesicles, while cytosolic Rac2 remains inactive in the guanosine diphosphate (GDP) bound state via interaction with RhoGDI (Ando et al, 1992). Upon the initiation of phagocytosis, GDP-Rac2 is converted to GTP-Rac2 through the activity of a Rac guanine nucleotide exchange factor. This allows for Rac2 translocation to the plasma or phagosomal membrane, thereby allowing the subsequent transit of cytochrome b558 from the vesicle to the membrane (Diebold and Bokoch, 2001). Concurrently, p47 phox is phosphorylated and undergoes a conformational change that now exposes two SRC-homology 3 regions to interact with the proline rich motif on p22 phox (Dusi et al, 1993). Furthermore, Phox homology domains on p47 phox allow for binding to phosphatidylinositol 3-phosphate (PI(3)P) and PI(3,4)P2, transient phosphoinositides that are generated only at the plasma membrane upon phagocytosis, thus, further stabilizing p47 phox localization to cytochrome b558 (Nauseef, 2004).

Among ROS sources, the NADPH oxidases are considered unique because from those components it is generated ROS in a highly regulated mode whereas ROS are generated as a by-product of enzymatic activity for all the other sources (Cave et al, 2006). Moreover, NADPH oxidases can stimulate further ROS production from one or more of the above enzymes, thereby being able to act as initiating sources of ROS. $O^{2\bullet-}$radical is the first moiety that is generated by NADPH oxidases (or most of the other sources) and can be rapidly dismutated to H_2O_2. The biological effects of ROS are expected to depend on the specific moiety generated, its localization and the relative balance between levels generated and the activity of antioxidant mechanisms; most signaling effects of ROS are considered to be mediated by H_2O_2 which is more stable and diffusible than $O^{2\bullet-}$.

XO is another potential source for ROS in vasculature. XO is a form of xanthine oxidoreductase that occurs in two different forms. The predominant form, xanthine dehydrogenase (XDH), can be converted into XO reversibly by direct oxidation of critical cysteine residues or irreversibly by proteolysis (Harris et al, 1999). XO is expressed mainly in the endothelium, and its expression and activity are enhanced by Ang II or oscillatory shear in a NADPH oxidase-dependent manner (Landmesser et al, 2007).

Mitochondrial electron transport generates $SO^{2\bullet-}$ as a side product of electron transport during oxidative phosphorylation. Most superoxide never escapes the highly reducing state of the mitochondrial matrix. If the $SO^{2\bullet-}$ generation is excessive, however, superoxide can escape to the intermembraneous space and cytosol via anion channels (Aon et al, 2004).

In summary, the investigation of the sources of reactive oxygen species is essential to describe new pathways involved in the pathogenesis of cardiovascular diseases as well as to develop new therapies to treat those disorders.

4. ROS in the heart

It is already known in the literature some mechanisms regarding the role of antioxidants during oxidative stress caused by ROS in the heart tissue. Among the enzymatic and non-enzymatic antioxidants involved in ROS-induced heart tissue injury we may include catalase, glutathione, SOD, ascorbid acid, melatonin, Vitamin C and E, among others. The antioxidant system in SHR cardiomyopathic hearts is induced, possibly due to events of enhanced ROS. This conditioning of the antioxidant system may help to overcome acute stress situations caused by ROS in the failing myocardium (Takimoto & Kass, 2007).

There are several potential sources of ROS in the heart with chronic heart failure (CHF). Excessive ROS derived from mitochondria have been shown in cardiomyocytes from experimental models of myocardial infarction and rapid pacing-induced heart failure (Ide et al, 2001). The enzyme xanthine oxidase produces $O^{2\bullet-}$ as a byproduct of the terminal steps of purine catabolism and recent studies suggest that it collaborates to oxidative stress in CHF. Xanthine oxidase expression and activity are enhanced in experimental models of CHF as well as in human end-stage CHF.

Nitric oxide synthase enzymes normally generate nitric oxide, but may instead generate $O^{2\bullet-}$ if this molecule becomes "uncoupled", a state that is mainly observed likely in the setting of lack of the BH4, which is a NOS cofactor or the NOS substrate l-arginine. NOS uncoupling and subsequent $O^{2\bullet-}$ production are implicated in the genesis of vascular endothelial dysfunction in patients with heart failure (Dixon et al, 2003).

In this context, infiltrating inflammatory cells are also an important source of ROS, mainly in conditions such as myocarditis and in the early stages after myocardial infarction. Recent evidence suggests that complex enzymes called NADPH oxidases are mainly important with regard to redox signalling in CHF and its antecedent conditions (Li et al, 2002). These enzymes catalyse electron transfer from NADPH to molecular oxygen, resulting in the formation of $O^{2\bullet-}$. NADPH oxidase activity has been found to be enhanced in experimental models of left ventricle hypertrophy and CHF as well as in end-stage failing human myocardium (Li et al, 2002).

Interestingly, ROS produced by NADPH oxidases can promote ROS generation by other sources, thereby increasing total levels of ROS. For instance, $O^{2\bullet-}$ from NADPH oxidase may oxidize and degrade BH4, thereby leading to NOS uncoupling, and this mechanism has been shown in diabetes and experimental hypertension (Verhaar et al, 2004). Similarly, NADPH oxidase-derived ROS may also activate xanthine oxidase (Li and Shah, 2004).

Previous studies have already investigated the relationship between the regulation of myocardial growth and death by NADPH oxidase. The classical phagocyte oxidase (gp91phox or Nox2) is also expressed in non-phagocytic cells in the heart, such as cardiomyocytes and fibroblasts (Bendall et al, 2002; Zhang et al, 2006). Activation of Nox2 requires stimulus-induced membrane translocation of cytosolic regulatory subunits, including p47phox, p67phox, p40phox, and Rac1, a small GTPase (Uhlinger et al, 1994). In resting cells, p47phox, p67phox, and p40phox form a ternary complex in the cytoplasm, whereas Rac associates with Rho-GDP dissociation inhibitor. When cells are stimulated with agonists for G protein-coupled receptors, such as angiotensin II (Ang II) type 1 receptors, p47phox is phosphorylated by protein kinase C, which in turn undergoes conformational

changes and allows the phox homology (PX) domain and the SH3 domain in p47phox to interact with phosphoinositides and p22phox in the membrane, respectively (Ago et al, 2004). As p67phox and p40phox interact with p47phox, this process leads to membrane translocation of p67phox and p40phox. Rac1 translocates to the membrane independently of p47phox and p67phox, where they form a functional complex with the Nox2-p22phox heterodimer, followed by a transfer of electrons to molecular oxygen (Quinn et al, 1993). Therefore, the activity of Nox2 is subjected to regulation through multiple mechanisms.

In relation to myocardial damage and NADPH oxidase, the loss of cardiomyocytes through apoptosis or necrosis causes impairment in cardiac function in the heart submitted to chronic myocardial infarction (Wencker et al, 2003). Oxidative stress is involved in the pathogenesis of apoptosis through various pathways, in which it is included activation of enzymes involved in pro-apoptotic signaling, for example, JNK, p38, ASK-1, and CaMKII (Matsuzawa and Ichijo, 2005), effects on the cellular anti-apoptotic signaling and direct effects of ROS on mitochondria, leading to cytochrome-c release.

Although excessive production of ROS by Noxs is detrimental, local and modest production of H_2O_2 and $O^{2\bullet-}$ by Noxs allows those component to function as signaling molecules, thereby mediating physiological responses. For instance, since Noxs are functional at low pO_2, Noxs may function as a sensor, and ROS generated by Noxs as a transducer, for hypoxia (Shiose et al, 2001). Erythropoietin (EPO) synthesis occurs in the renal tubular cells, where Nox4 is abundantly expressed (Lacombe et al., 1988). Since DPI, an antioxidant drug, not only blocks oxygen sensing but also inhibits Nox4 in renal tubular cells, it has been proposed that Nox4 is an O_2 sensor in the kidney and may regulate EPO production. The causative role of Nox4 in mediating EPO synthesis through its function as an O_2 sensor remains to be shown. Recently, a role of Nox4 in mediating angiogenesis during cardiac hypertrophy was reported. Pathological hypertrophy induces upregulation/activation of Nox4, which in turn causes stabilization of HIF-1α, upregulation of VEGF, and increases in angiogenesis (Zhang et al, 2006). It appears that the protective effect of Nox4 prevails under the authors' experimental conditions. It remains unknown, however, whether such a mechanism is sufficient to overcome increases in cell death and mitochondrial dysfunction directly caused by upregulation of Nox4 in response to hypertrophic stimuli (Ago et al, 2003).

In addition, the regulation of Ca^{2+} level in cardiac myocytes is centrally important not only in excitation–contraction coupling but also in many other processes such as the regulation of gene expression and cellular energetics. ROS are recognized to be capable of influencing cellular Ca^{2+} regulation at several levels, notably via redox alterations of key amino acid residues involved in the function and gating properties of intracellular and plasma membrane ion channels and transporters — e.g., L-type channels, the Na^+/Ca^{2+} exchanger, the sarcoplasmic reticulum (SR) ATPase (SERCA) and the ryanodine receptor (Hool and Corry, 2007). Recent studies have started to address the role of NADPH oxidase-derived ROS in these effects.

It has been reported that ryanodine receptor-mediated Ca^{2+}-induced Ca^{2+} release in rat cardiac myocytes is inhibited by an endogenous NADH oxidase activity in the SR, although the molecular nature of this oxidase was not established (Cherednichenko et al, 2004). In contrast to this study, Sanchez et al. (2008) reported the presence of Nox2 NADPH oxidase activity in canine cardiac SR and showed that oxidase activation enhanced S-

glutathionylation of ryanodine receptors and hence SR Ca^{2+} release — effects which were abrogated by apocynin (a purported Nox inhibitor, but which may act as a non-selective antioxidant). The same group also showed that oxidase activity and the effects on SR Ca^{2+} release were augmented by tachycardia (Sanchez et al, 2008). $O^{2\bullet-}$radical production by NADPH oxidase on the SR of bovine coronary artery smooth muscle cells has also been shown to regulate calcium-induced calcium release (Yi et al, 2006). In isolated cardiac myocytes, plasma L-type Ca^{2+} channel open-state probability was reportedly enhanced by endothelin-1 together with enhanced NADPH oxidase activity, effects which were abolished in cardiomyocytes pre-treated with a specific NADPH oxidase inhibitor, gp91ds-tat (Zeng et al, 2008). These studies suggest that NADPH oxidases may acutely regulate at least two channels directly involved in intracellular Ca^{2+} homeostasis, i.e. the L-type Ca^{2+} channel and the ryanodine receptor.

In summary, Figure 3 presents the main mechanisms involved in ROS-induced cardiovascular disorders. Many studies implicate ROS-generating NADPH oxidases in redox signaling in cardiovascular cells and involvement in pathological processes such as cardiac hypertrophy, fibrosis, apoptosis and ventricular remodeling.

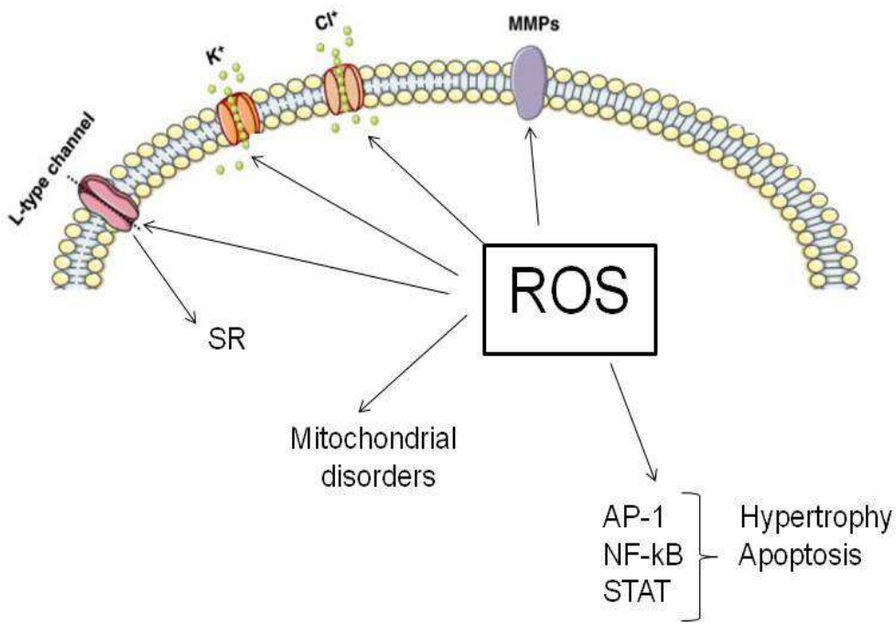

Fig. 3. Main mechanisms involved in the potential effects of NADPH oxidase-derived ROS in the cardiac myocyte. SR: sarcoplasmic reticulum; MMPs: matrix metalloproteinases; CICR: calcium-induced calcium release.

5. ROS-Induced vascular damage

ROS are involved in pathological and physiological processes in the vasculature. Enhanced arterial pressure is partially caused by enhanced total peripheral vascular resistance, which is due to disorders of structural remodeling of blood vessels and vasomotor function. Vascular diseases including coronary artery disease, cerebrovascular and peripheral

vascular diseases are the largest cause of mortality and morbidity in industrialized countries. Many common risk factors for vascular disease, such as hypertension and diabetes, remain prevalent in Western and other populations, suggesting that vascular disease will continue to impose a substantial burden on health care resources throughout the next generation. The earliest detectable changes in vascular disease states are irregularities of the endothelium, resulting in loss of the endothelium normal homeostatic functions that normally act to inhibit disease-related processes such as inflammation and thrombosis. In particular, nitric oxide (NO) produced by NO synthase (eNOS) in the vascular endothelium modulates blood flow and pressure (Umans & Levi, 1995) and has important antiatherogenic effects on platelets, vascular smooth muscle and endothelial cells.

It is known that ROS causes vascular tone increase, because it influences endothelium regulatory role and also due to its effects on vascular smooth muscle contractility. By influencing phenotype regulation of vascular smooth muscle cells, death of vascular cells, cell migration, atypical growth, and extracellular matrix (ECM) reorganization, ROS collaborate to vascular remodeling (Lee & Griendling, 2008).

The fact that nitric oxide (NO) is scavenged by superoxide suggests that superoxide production may in part underlie endothelial dysfunction in human atherosclerosis, as it does in some experimental models of vascular disease.

In vitro (Lambeth et al, 2000) and in vivo (Vita et al, 1990) studies indicate that ACh-mediated vasorelaxations in human vessels are inversely related to the number of atherosclerotic risks factors present. Nonetheless, functional studies of human vascular superoxide production have been more limited (Lambeth et al, 2000). It was found large variability in both NO mediated vascular relaxations and basal superoxide production in internal mammary arteries (Huraux et al. (1999), however, there was no consistent associations between these two parameters or with clinical risk factors (Lambeth et al, 2000).

It was investigated superoxide production by NAD(P)H oxidase in human vessels and the relationships between superoxide production, atherosclerotic risk factor profile and endothelial dysfunction. It was reported the expected inverse correlation between risk factor profile and NO-mediated endothelium-dependent relaxations in vessel ring isometric tension studies. However, it was also found that superoxide production by NAD(P)H oxidases progressively enhanced with increasing risk factor profile (Guzik et al, 2000). Furthermore, NAD(P)H oxidase-mediated superoxide production was inversely correlated with NO-mediated vasorelaxations in individual patients, such that patients with the highest superoxide production had the most deficient endothelial function.

The association between enhanced vascular NAD(P)H oxidase activity and impaired endothelial vasorelaxations may be due to direct scavenging of NO by superoxide, as has been demonstrated in animal model systems. However, the both could result independently from increasing exposure of endothelium, media and adventitia to factors acting through different signaling pathways. Alternatively, superoxide may directly modulate NO-mediated vascular signaling, for instance by peroxynitrite-induced nitration of G proteins or other membrane components (Feron et al, 1999). Previous data suggest that G protein-coupled receptor function is deficient in atherosclerosis (Liao & Clark, 1995). Previous observation that vasorelaxations to ACh were significantly lower than maximal relaxations

to the calcium ionophore A23187 is consistent with this hypothesis, and with observations in human internal mammary arteries (Hurax et al, 1999). Nevertheless, the significant correlation between ACh and A23187 - induced relaxations, and the association of NADH-dependent superoxide production with both ACh and A231287- stimulated vasorelaxations suggest that a change in G protein-coupled receptor signaling is unlikely to be the sole mechanism underlying decreased NO-mediated vasorelaxations, as A23187 activates endothelial NO synthase independently of any receptor mediated pathway. Alternatively, superoxide may impair endothelial function by direct effects on endothelial NO synthase activity, (Peterson et al, 1999), possibly mediated through oxidation of the NOS cofactor, tetrahydrobiopterin (BH4).

Many studies have focused on the potential role of BH4 oxidation different oxidized biopterin species in reducing BH4 bioavailability for eNOS (Figure 4).

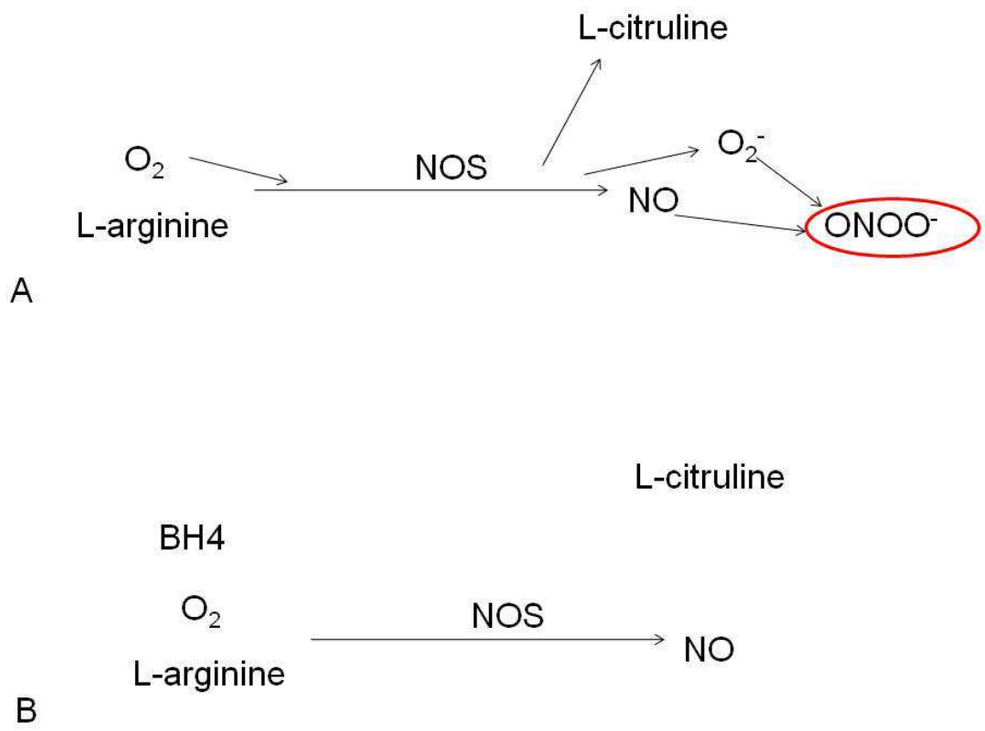

Fig. 4. Schematic representation of nitric oxide synthase (NO synthase) reaction leading to l-citrulline and nitric oxide (NO) from l-arginine and oxygen (O_2) without (A) and with BH4 (B). It is important to note that this reaction without BH4 increases ROS.

Although superoxide can indeed react directly with BH4, the rate constant of this reaction is many orders of magnitude lower than that for NO with superoxide (Vasquez-Vivar et al, 2002). A more likely mechanism for BH4 oxidation is the interaction with peroxynitrite (generated from the interaction between NO and superoxide). It was indicated that peroxynitrite can oxidize BH4 within minutes at physiologically relevant concentrations (Crabtree et al, 2011). EPR (electron paramagnetic resonance) spectroscopy experiments

have demonstrated that peroxynitrite oxidizes BH4 to the (non-protonated) BH3 (trihydrobiopterin) radical, and then to BH2, with a rate constant estimated to be 6 × 103 M−1 s−1, several-fold higher than reactions between peroxynitrite and ascorbate, glutathione or thiol groups (Gao et al, 2009). Oxidation not only directly reduces BH4 bioavailability, but the oxidation products themselves (such as BH2), which have no cofactor activity, may compete with BH4 for binding to endothelial NOS (eNOS) (Crabtree et al, 2008).

ROS are also involved in vascular remodeling. Vascular remodeling is defined as alteration of structure leading to alteration in wall thickness and lumen diameter. It can be induced through passive adaptation to chronic changes in hemodynamics and/or through neurohumoral factors including Ang II and ROS. The progression of hypertension involves two different types of vascular remodeling: inward eutrophic remodeling and hypertrophic remodeling (Schiffrin, 2004). Eutrophic remodeling is characterized by decreased lumen size, thickening of the media, enhanced media:lumen ratio and, usually, little change in medial cross-sectional area. In this case, the change in vascular smooth muscle (VSMC) size is negligible (Korsgaard et al, 1993), and medial growth toward the lumen is mainly mediated by reorganization of cellular and non cellular material of the existing vascular wall, accompanied by enhanced apoptosis in the periphery of the blood vessel (166). This is common in small resistance arteries of essential hypertensive patients and SHR (Korsgaard et al, 1993).

On the other hand, hypertrophic remodeling characterized by an increase in wall cross-sectional area predominates in conduit arteries of secondary hypertension, such as those of renovascular hypertensive patients or Ang II-infused hypertensive rats. An increase in cell size and enhanced accumulation of ECM proteins such as collagen and fibronectin are specific features of hypertrophic remodeling (Rizzoni et al, 2000). Hence, VSMC hypertrophy and ECM synthesis are required for hypertrophic remodeling. Both mechanical wall stress and humoral mediators such as Ang II collaborate to hypertrophic remodeling (Rizzoni et al, 2000).

The both forms of remodeling frequently coexist in different vascular beds and at different stages of hypertension, which occurs even in the same subject. Even though the determinants of each type of remodeling have not been clearly described, the reorganization of media mediated by phenotype modulation of VSMCs, migration, cellular growth, apoptosis, and ECM production and rearrangement is thought to be common to both processes. These events occur cooperatively and simultaneously.

Thus, it is not easy to distinguish contributions of each component in vivo. Vascular remodeling is improved by treatment with tempol, antioxidant vitamins (Chen et al, 2011), Ang II receptor antagonists, or NADPH oxidase inhibitors in animal experimental models, as well as in clinical trials (Zhou et al, 2005), emphasizing the role of ROS.

Recent studies with improved forms of ROS scavenging enzymes, specific inhibitors for different ROS generating enzymes, and redox signaling pathway blocking agents allow subtle modulation of redox signaling and may overcome the redundancy of general antioxidant treatments. Therefore, the spatial and temporal aspects of redox signaling in the vasculature are of much importance to understand the etiological role of ROS and to develop better strategies to treat hypertension.

6. Oxidative stress in the kidney

Renal artery obstruction can cause arterial hypertension, which is followed by impaired renal function and renal atrophy. Cardiovascular disorders caused by kidney injury are in part regulated by renin release from the stenotic kidney, with a subsequent increase in angiotensin II (Ang II) synthesis (Trinquart et al, 2010). Ang II results in the activation of $O^{2\bullet-}$ generation through nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, a multi-subunit enzyme, which is one of the enzymatic sources of $O^{2\bullet-}$ (Chabrashvili et al, 2002).

The mechanism(s) by which ANG II produces superoxide is not entirely elucidated yet. However, Mollnau et al. (2002) found that ANG II infusion during seven days enhanced expression of nox 1, gp91(phox), and p22(phox) subunits of NADPH oxidase via a PKC system. The mechanism which involves ANG II-mediated increase in the release of superoxide locates into activity a series of events that may play relevant functions in increased blood pressure.

Previous studies were conducted in attempt to clarify the specific components of ROS that are involved in the development of ANG II-induced hypertension. Haas et al. (1999) are among the first to demonstrate that the slow hypertensive response to ANG II was accompanied by a significant elevation of ROS as estimated indirectly by increases in plasma F2-isoprostanes, an oxidative metabolite of arachidonic acid (Morrow et al, 1990). Nishiyama et al. (2002) also demonstrated that a prolonged infusion of ANG II in rats stimulates ROS production. In this study, the administration of tempol, a SOD mimetic, reversed the vasoconstriction and produced vasodilation via an NO-dependent mechanism.

Ortiz et al. (2011) found in rats that the development of slow pressor responses to ANG II could be inhibited by the administration by antioxidants such as tempol and vitamin E. As a result of antioxidant treatment, there was a fall in renal blood flow and glomerular flow rate, whereas the indexes of oxidative stress, TBARS, and isoprostanes were found to be decreased in peripheral circulation as well as the renal vein.

Some investigations suggest that the decrease in the NO concentration due to interaction with superoxide anon radical constitutes a major component in the development of the observed vasoconstriction. Supporting the assumption that inhibition of NO synthesis enhances the vasoconstrictor effect of ANG II are the studies of Kitamoto et al. (2000). These investigators found that the continuous administration of l-NAME (a NOS inhibitor) to Sprague-Dawley rats for seven days induced ROS production, which was dependent on ANG II, because the effect was blocked by the administration of ANG II receptor blockers. Relevant to these findings are the studies of Usui et al. (1999), who also found an increase in ROS produced byl-NAME, which was blocked by the administration of antioxidants. In this study, l-NAME blockade was associated with an increase in angiotensin converting enzyme activity in the aorta. The studies of Kitamoto et al. (2000) and Usui et al. (199) reveal an interesting aspect of ANG II, NO, and oxidative stress. They suggest that a simple decrease in NO synthesis leaves unbalanced ANG II, which induces ROS release. This situation will be further stimulated by the increase in converting enzyme activity, which can accelerate the production of ANG II causing a positive feedback for oxidative stress.

The question of whether NO inhibition alone can cause ROS production without the participation of ANG II should be further explored. As mentioned previously, NOS can

produce superoxide when BH4 is oxidized to BH4, leading to an increase in ROS and a reduction in NO (Figure 4). This could set up a vicious cycle that accentuates NO dysfunction and tends to perpetuate oxidative stress. These alterations may constitute an important mechanism of dysregulation that produces hypertension and renal dysfunction (see later). An example of this alteration is the SHR in which blood pressure can be normalized by the administration of BH4 (McIntyre et al, 1997).

Researches performed in the renovascular model of hypertension in rats have shown relevant data regarding the relationship between oxidative stress and hypertension. The central regulation of the sympathetic nervous system (SNS)

involved in cardiovascular regulation is complex, involving multiple reflex pathways and neural connections with a large number of neurotransmitters and neuromodulators acting in specific groups of neurons in the central nervous sysem (CNS) involved in the tonic and reflex control of the cardiovascular system. In the CNS, Ang II is able to increase sympathetic vasomotor tone and blood pressure, and is involved in the pathogenesis of many experimental models of hypertension. Thus, the close functional association between NADPH oxidase and the Ang II is of particular relevance in linking oxidative stress in the brain to sympathoexcitation and hypertension (Campos, 2009). For instance, intracerebroventricular infusion of NADPH oxidase inhibitor antagonizes the pressor response induced by centrally mediated Ang II actions (Gao et al, 2004).

In the brain, the overexpression of SOD, an enzyme responsible for O_2 breakdown, also abolishes the central pressor effect of the octapeptide (Zimmerman et al, 2004) suggesting that in the CNS there is a positive correlation between the increase in ROS and the central pressor response mediated by Ang II. Considering that the paraventricular nucleus of the hypothalamus (PVN) and the rostroventrolateral medulla (RVLM) contain critically important neurons involved in the control of sympathetic vasomotor tone and arterial pressure (Colombari et al, 2001).

Previous studies reviewed and examined whether there was an increase in AT1 receptor expression and oxidative stress markers within these two nuclei in 2K1C hypertension. NAD(P)H oxidase subunits (p47phox and gp91phox) and antioxidant enzyme CuZnSOD mRNA expression were quantified in the RVLM and PVN of 2K1C hypertensive rats. It was hypothesized that the overactivity of NADPH oxidase-derived ROS associated with a reduction in the activity of CuZnSOD within the RVLM and PVN could collaborate to 2K1C hypertension, particularly in the renin-dependent phase of hypertension.

In summary, the recent studies support the idea that an increase in ROS in the kidney is involved in the development of cardiovascular disorders, playing a major role in maintaining high arterial pressure and sympathetic drive under conditions of renovascular hypertension.

7. The involvement of the nervous system in ROS-induced cardiovascular disease

Neurons in the brain present increased density of polyunsaturated fatty acids in its cell membranes. Fatty acids are targets of free radicals. An indirect marker of ROS, TBARS is enhanced in the brainstem of SPSHR compared to age-matched control (Hirooka, 2008). Others reported enhanced ROS in the brainstem of rabbits with heart failure (Gao et al, 2007).

The activity of sympathetic and parasympathetic systems, which are both involved in cardiopulmonary reflex, as well as the cardiovascular regulation, is under the control of a medullary circuitry comprising the nucleus of the solitary tract (NTS), rostral (RVLM) and caudal ventrolateral medulla (CVLM) and the nucleus ambiguous. Drugs injection into the fourth cerebral ventricle (4th V) may easily reach structures surrounding the ventricular system like the area postrema and the dorsal motor nucleus of the vagus (Colombari et al, 2001) (Figure 5). Those areas are also involved in cardiovascular reflex responses, in which we may include baroreflex (Valenti et al, 2009a; Valenti et al, 2009b; Cisternas et al, 2010).

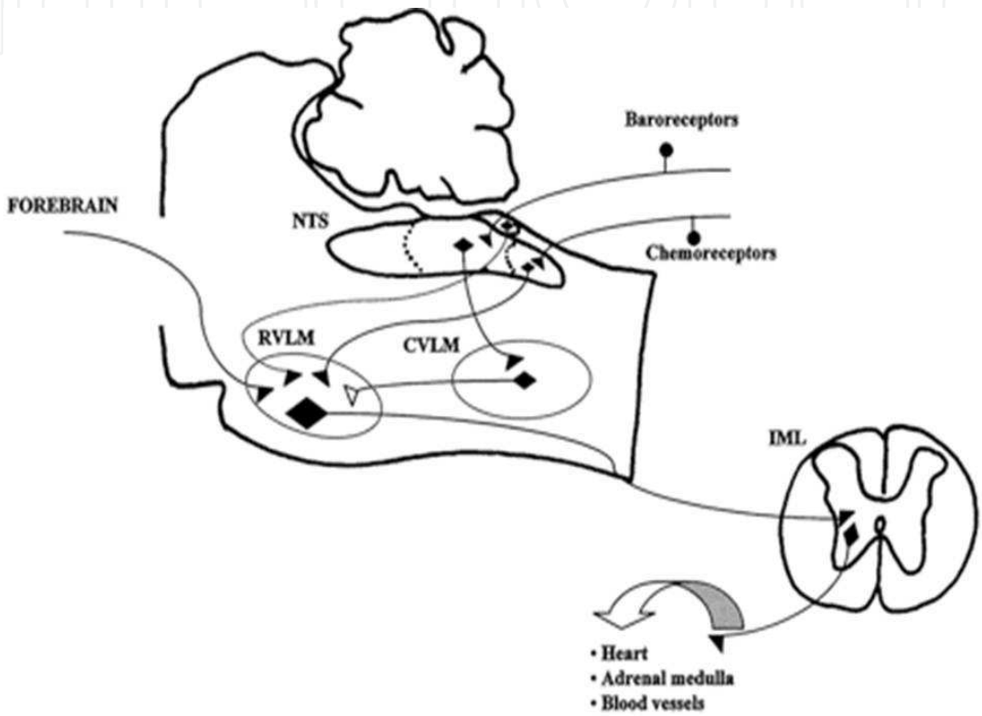

Fig. 5. Schematic sagittal view of the medulla oblongata showing brain pathways implicated in neurogenic hypertension. Premotor neurons from the RVLM send excitatory synapses to preganglionic neurons situated in the intermediolateral cell column (IML), providing sympathetic efference to target organs. The RVLM is the group of neurons that receive excitatory afference from the commissural nucleus of the solitary tract (NTS) and area postrema. It also receives inhibitory afferences from the caudoventrolateral medulla (CVLM). Adapted from Valenti et al, 2007.

A previous investigation suggested that brain ROS is associated with enhanced sympathetic activity (Gao et al, 2007) and systemic ROS is also related to impaired baroreflex (Bertagnolli et al, 2006). In addition, it was reported increase of NAD(P)H oxidase activity and expression into the RVLM, the primary central site for the maintenance of sympathetic nerve activity, in CHF rabbits. In the same sequence of procedures, the same authors observed that a reduction of brain $O^{2\bullet-}$ by tempol, a SOD mimetic, decreased the sympathetic outflow in chronic heart failure rabbits. Conversely, an increase of central $O^{2\bullet-}$ due to administration of the SOD inhibitor diethyldithiocarbamic acid enhanced the

sympathetic outflow in both normal and chronic heart failure rabbits (Gao et al, 2007). Taken together, those data suggest that antioxidant enzymes, i.e., SOD and catalase, into the brainstem are involved in baroceptor reflex regulation, since baroreflex is modulated by sympathetic and parasympathetic activity (Valenti et al, 2009a).

Recent studies from our laboratory have investigated the effects of ROS into the fourth cerebral ventricle (4th V) on cardiovascular responses.

In one study (Valenti et al, 2011a) it was evaluated the effects of 3-amino-1,2,4-triazole (ATZ), a catalase inhibitor, into the 4th V on baroreflex components in conscious rats. It was revealed that this drug significantly attenuated bradycardic and tachycardic reflex, bradycardic peak and it also decreased heart rate range 30 minutes after its injection. While in Wistar rats treated with vehicle (saline 0.9%) there were no significant changes regarding baseline mean arterial pressure (MAP) and heart rate (HR) and baroreflex components. Considering that the tachycardia (tachycardic reflex) in response to SNP is mediated by both sympathetic and parasympathetic activity (Stornetta et al, 1987) and that we reported reduction in the maximal parasympathetic responses to elevation in mean arterial pressure, while there were no changes in tachycardic peak response to decrease in mean arterial pressure (highest sympathetic response), we suggest that ATZ into the 4th V is acutely involved with parasympathetic activity but is not involved in baroreflex changes. The lack of any change in the vehicles groups is consistent with this assumption. In view of the anatomical scope of the 4th V, an action on an only one neuronal cluster is not an easy accomplishment. However, prior researches indicated a preference for parasympathetic system which modulates HR, such as the dorsal motor nucleus of the vagus and nucleus ambiguous, which receive glutamathergic projections from the nucleus of the solitary tract (Colombari et al, 2001).

In another study (Valenti et al, 2011b), it was evaluated the effects of catalase inhibition into the 4th V on cardiopulmonary reflex in conscious Wistar rats. In this method, we used male Wistar rats, which were implanted with a stainless steel guide cannula in the 4th V. The femoral artery and vein were cannulated for MAP and HR measurement and for drug infusion, respectively. After basal mean arterial pressure and heart rate recordings, the cardiopulmonary reflex was tested with a dose of phenylbiguanide (PBG, 8 µg/kg, bolus). Cardiopulmonary reflex was evaluated before and 15 minutes after 1 µl of ATZ (0.01 g/100 µl) injection into the 4th V. Vehicle treatment did not change cardiopulmonary reflex responses. ATZ injected into the 4th V significantly enhanced hypotensive responses without influencing the bradycardic reflex. Taken together, those data suggested that ATZ injected into the 4th V increases sympathetic inhibition but does not change the parasympathetic component of the cardiopulmonary reflex in conscious Wistar rats.

Nevertheless, opposite findings were found in SHR. Another study (Valenti et al, 2011c) was undertaken to evaluate the acute effects of central n-acetylcysteine, an antioxidant drug, on baroreflex in juvenile SHR and age-matched Wistar Kyoto (WKY) rats. It was observed that n-acetylcysteine injection into the 4th V did not significantly change baroreflex gain, bradycardic and tachycardic reflex, bradycardic and tachycardic peak in SHR and WKY rats. Interestingly, n-acetylcysteine caused slight but significant increase in basal heart rate 15 minutes after its injection in conscious WKY rats.

Many previous studies have already demonstrated the effects of oxidative stress in cardiovascular reflex. Zanzinger and

Czachurski (2009) demonstrated that SOD injected into the RVLM decreased sympathetic nerve activity in swine. Several groups have now shown that ROSs stimulate sympathetic outflow (Campese et al, 2004). Campos et al (2011) evidenced that the lack of LDL receptor enhanced cholesterol blood levels, enhanced ROS and impaired baroreflex sentivity. Monahan et al (2007) supported the hypothesis that oxidative stress collaborates to age-associated decreases in cardiovagal baroreflex sensitivity in healthy men. On the other hand, Wright et al (2009) indicated that in male smokers, circulating antioxidants had no effect on baroceptor reflex function and minor effects on the cardiovascular system were seen following acute fat and vitamin ingestion.

In the central nervous system, the complex regulating blood pressure is contained within topographically selective networks characterized at all levels of the neuraxis. Adjustments in this modulation network may lead to labile changes in autonomic function. The development of neurogenic hypertension may involve improper alterations in synaptic function within these networks. Thus, investigations regarding the relationship between the nervous system and the cardiovascular system and its importance to regulation of the physiologic homeostasis are always welcome in the basic and clinical research.

8. Perspectives

At the moment, relevant milestones were achieved with the availability of more overt facts that demonstrates that cardiovascular disorders mechanisms are linked to ROS increase and dysregulation of oxidant-antioxidants systems. The oxidation and nitration of cellular lipids, proteins and nucleic acids, and formation of aggregates of oxidized molecules underlie the loss of cellular function, cellular ageing and the inability of cells to withstand physiological stresses. Moreover, ROS regulate energy metabolism and signal transduction mechanisms in response to situations of nitrosativeor or oxidative stress. Sources of ROS, physiological and pathophysiological conditions, and cellular oxidant targets determine the profile nature of a disease process and resultant outcomes.

In summary, the data presented in this chapter is significant to the literature, because progress in redox signaling provides insight into the function of ROS in the pathological and physiological mechanisms involved in cardiovascular disorders. Nonetheless, the literature raises more questions. Regarding hypertension treatment, there are a few points to be underscored. ROS act as signaling molecules associated with diverse physiological mechanism which are indispensable for normal function of the brainstem. Inappropriate modulation of ROS impairs redox signaling, which is assumed to stimulate pathologic situations, in which we may include hypertension. Moreover, our study reinforces the importance to investigate the integrative neuroscience.

9. Concluding remarks

Advances in ROS signaling provide insight into the role of ROS in the pathological and physiological mechanisms related to cardiovascular disorders. The comprehension of how redox state regulates the cardiovascular system is a relevant step for a best explanation for

the mechanism involved in antioxidant species applied in clinical therapies. Therefore, the presentation of data regarding the systems different from the cardiovascular system implicated in ROS-induced cardiovascular diseases is relevant to the integrative physiology and more particularly to control physiology and clinical therapies that aim to prevent cardiovascular disorders such as hypertension and heart failure.

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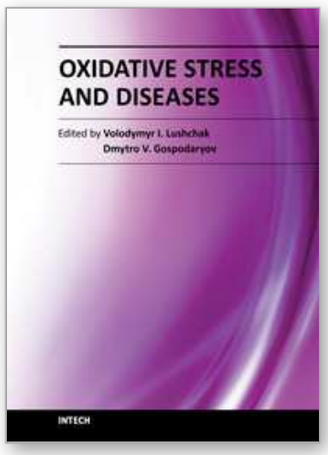

Oxidative Stress and Diseases

Edited by Dr. Volodymyr Lushchak

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The development of hypothesis of oxidative stress in the 1980s stimulated the interest of biological and biomedical sciences that extends to this day. The contributions in this book provide the reader with the knowledge accumulated to date on the involvement of reactive oxygen species in different pathologies in humans and animals. The chapters are organized into sections based on specific groups of pathologies such as cardiovascular diseases, diabetes, cancer, neuronal, hormonal, and systemic ones. A special section highlights potential of antioxidants to protect organisms against deleterious effects of reactive species. This book should appeal to many researchers, who should find its information useful for advancing their fields.

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