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Review Article

Hydrogen peroxide signaling in vascular endothelial cells

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ABSTRACT

Redox signaling is implicated in different physiological and pathological events in the vasculature. Among the different reactive oxygen species, hydrogen peroxide (H_2O_2) is a very good candidate to perform functions as an intracellular messenger in the regulation of several biological events.
In this review, we summarize the main physiological sources of H_2O_2 in the endothelium and the molecular mechanisms by which it is able to act as a signaling mediator in the vasculature.

Introduction

Endothelial cells (ECs) line the inner surface of the cardiovascular system acting as a natural barrier between the blood and the rest of organs and tissues. This metabolically active monolayer organ is constantly exposed to different biomechanical and biochemical stimuli to which it responds by preserving the integrity and homeostasis of vascular function [1]. Accumulating evidence indicates the important role of redox signaling in the triggering and mediation of these actions. Historically, oxidative stress and thus, the increased production of reactive oxygen species (ROS), have been closely related with endothelial dysfunction, with involvement in the pathogenesis of several cardiovascular diseases such as hypertension, diabetes or atherosclerosis among others [2–5]. However, a large body of research has demonstrated a key role for ROS as physiological regulators of intracellular signaling pathways involved in the function of vascular endothelium [6].

Redox signaling

For many years, ROS were described as unwanted toxic products of cellular metabolism able to cause molecular damage (including DNA, proteins and lipids), cell and tissue dysfunction. Substantial evidences in the past decades have proved that although high oxidant exposure or low antioxidant defense are implicated in the pathogenesis of several cardiovascular diseases such as atherosclerosis, hypertension or diabetes, ROS are important *signaling* molecules playing an essential role in the regulation of a large variety of different cell signaling processes [6–8].

Although the term ROS include all the chemical species derived from the incomplete reduction of molecular oxygen (O_2), it is important to mention that different redox-active species have completely different biological properties including reactivity, half-life or lipid solubility that have important implications in their action. Thus, the specificity and the selectivity of the different ROS are dictated by their chemical reactivity [9].

Among the different ROS, hydrogen peroxide (H_2O_2) fulfills the prerequisites for serving as an intracellular messenger and acting as a cell-signaling molecule. H_2O_2 is a small and non-polar molecule able to diffuse across biological membranes. It is ubiquitously produced and its longer half-life makes it suitable to act as a second messenger exerting prolonged effects in different signaling pathways [10].

To better understand the role and the effect of H_2O_2 in redox signaling it is critical to focus on the main sources of H_2O_2 in the vasculature and on the nature of this ROS as a two-electron oxidant.

Sources of hydrogen peroxide in the endothelium

Intracellular generation of ROS in endothelial cells both occur under physiological as well as pathophysiological conditions. In the endothelium it predominantly arises from four enzymatic systems which include the different isoforms of NAPDH oxidases (NOXs, see below for precisions), xanthine oxido-reductase, uncoupled endothelial nitric oxide synthase (eNOS) and mitochondrial respiration complexes [1,2]; however other sources such as the arachidonic acid metabolizing enzymes lipoxygenase and cyclooxygenases or the cytochrome P450 have been also described [11] (Fig. 1).

All these sources primarily catalyze the reduction of molecular oxygen after the acceptance of one electron and lead to the formation of superoxide radical anion ($O_2^{\bullet-}$), a ROS extremely unstable that dismutates to H_2O_2 either spontaneously or enzymatically catalyzed by superoxide dismutase. Of note, some enzymes, such as glucose oxidase or xanthine oxidase have been described to directly produce

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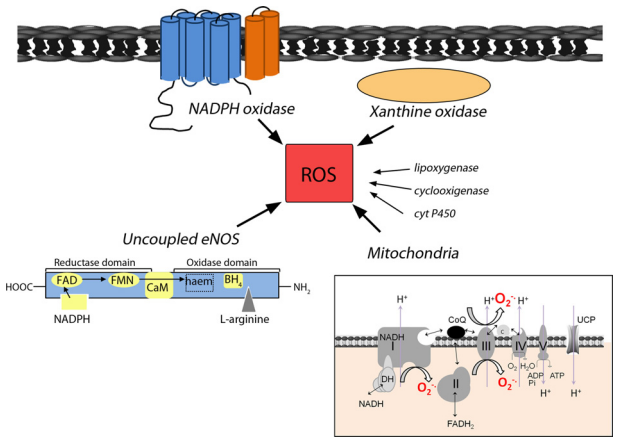

Fig 1. Sources of reactive oxygen species in the vascular endothelium.The major sources of ROS in the endothelium include NADPH oxidase isoform 4, eNOS uncoupling, mitochondrial respiration and xanthine oxidase. Other sources such as lipoxygenase, cyclooxygenase or cytochrome P450 also contribute to ROS generation in the vascular endothelium.

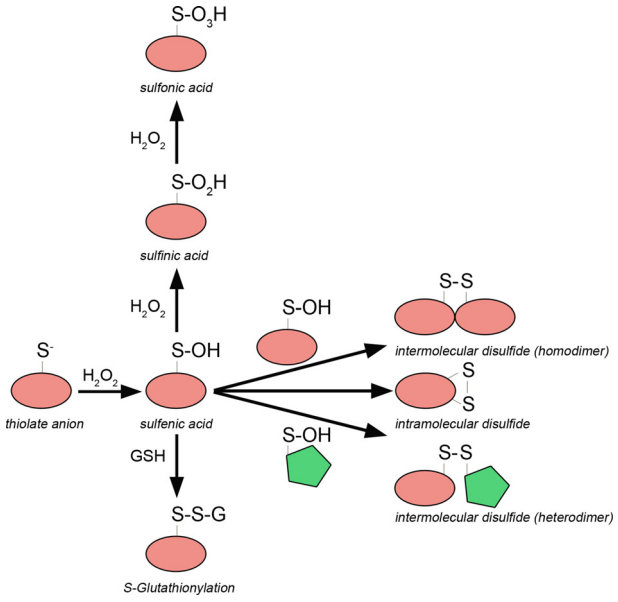

Fig 2. Protein thiol modifications by hydrogen peroxide.H_2O_2 induces cysteine dimerization (R–S–S–R) via the formation of the unstable intermediate sulfenic acid (R–SOH). Disulfides can form between cysteines located in the same protein (intramolecular disulfides), in different proteins (intermolecular disulfides), or between the protein thiol and glutathione (S-glutathionylation). In the presence of high concentrations of H_2O_2, the sulfenic acid can become further oxidized to sulfinic (R–SO_2) or sulfonic (R–SO_3) acid.

H_2O_2 by donating two electrons to oxygen [11]. In the case of the NOX4 isoform (the most abundant NADPH oxidase in the endothelium), there is some controversy about the ROS produced. Whereas some groups have described NOX4 as the only vascular homolog that directly produces H_2O_2 [12], others have proposed that the $O_2^{\bullet-}$ produced by NOX4 is rapidly converted to H_2O_2, which becomes almost undetectable [13] (Fig. 2).

The main features of these enzymes are summarized as follows:

NADPH oxidase

In contrast to other oxidases which produce ROS as a byproduct of their catalytic function, NOX family enzymes have no known biosynthetic or catabolic function but synthesize ROS as their primary function [14,15]. They are a family of seven trans-membrane electron transporters that catalyze the transfer of electrons across biological membranes from the electron donor NADPH to O_2, leading to the generation of $O_2^{\bullet-}$ [16] and according to some reports H_2O_2 [12,17,18]. All NOX isoforms have six trans-membrane alpha helices with cytosolic N- and C-termini and they are differentially expressed and regulated in specific tissues. In endothelial cells, whereas NOX1, NOX2, NOX4 and NOX5 isoforms have been identified under physiological and pathophysiological conditions [19], NOX4 is by far the most abundant NADPH isoform [20,21]. In addition this isoform is the most distantly related member of the family. While its activity is dependent on p22phox, it does not require any cytosolic subunits such as p47phox, p67phox, p40phox or Rac, as other NOX isoforms do [22].

Xanthine oxidoreductase

Xanthine oxidoreductase, termed as xanthine oxidase (XOR), is another potential source for ROS in the vasculature [23]. It is an iron–sulfur molybdenum flavoprotein enzyme that catalyzes the last steps of purine metabolism, the transformation of hypoxanthine and xanthine to uric acid, with $O_2^{\bullet-}$ or H_2O_2 generation as by-products [24]. It exists in two forms, as xanthine dehydrogenase (XDH) and as xanthine oxidase (XO) [25]. The XDH activity present in the vascular endothelium is converted into XO by processes including thiol oxidation and/or proteolysis. The ratio between XO and XDH in the cells is critical to determine the amount of ROS produced by these enzymes [26]. Increases both in the expression and activity of XO have been related to vascular diseases [27,28]. In the last decade, XOR has been proposed as capable to produce NO• itself [29,30] adding a new essential vascular role for this enzyme in biological tissues [25].

Uncoupled eNOS

NO• is produced in mammals by a family of nitric oxide synthase (NOS) enzymes. There are three different isoforms, two of them constitutively present (the endothelial nitric oxide synthase, eNOS or NOS3, and the neuronal nitric oxide synthase, nNOS or NOS1), and one which is inducible (iNOS or NOS2). They are all flavin- and heme-containing enzymes that act as homodimers shuttling electrons from the NADPH bound at the C-terminal (reductase domain) to the N-terminal heme (oxidase domain), reducing O_2 and incorporating it into the guanidine group of L-arginine to produce L-citrulline and NO•. However, in the absence of cofactors (L-arginine, tetrahydrobiopterin (BH4) or both) NOSs can become a source of $O_2^{\bullet-}$ in endothelium [31], thus becoming "uncoupled" to their primary role of NO• synthesis. This uncoupling involves the conversion of NOS enzyme to a monomer which generates $O_2^{\bullet-}$ instead of NO• [32]. Uncoupling of eNOS has been related to different cardiovascular diseases that concur with endothelial dysfunction such as atherosclerosis, hypertension, hypercholesterolemia or diabetes [33–36].

Mitochondria

Mitochondria represent the major intracellular source of ROS under physiological conditions. Notwithstanding, ROS production by mitochondria can also be enhanced by several intracellular stimuli. Mitochondrial ROS production is a consequence of oxidative phosphorylation linked to aerobic respiration within the mitochondrial electron transport chain (ETC). This machinery is situated in the inner mitochondrial membrane and it is able to catalyze electron transfer using more than 80 peptides organized in four complexes [37]. The transfer of electrons usually leads to the formation of ATP by the fifth complex; however, at eight different sites along the respiratory chain, electrons derived from NADH or FADH can directly react with oxygen and generate $O_2^{\bullet-}$ [38]. Electron leakage from the ETC causes partial reduction of molecular oxygen to $O_2^{\bullet-}$ instead of reduction to H_2O. It is predicted that 1–2% of the O_2 consumed is converted into ROS [39]. Mitochondrial $O_2^{\bullet-}$ dismutation by MnSOD leads to

the formation of H_2O_2 inside the mitochondria [40]. The tight regulation of mitochondrial ROS is essential for avoiding the accumulation of ROS and oxidative damage, thus permitting the signaling role of these species. Although the function of mitochondrial H_2O_2 in several redox-dependent processes has been extensively reviewed [41,42], data in human vasculature are very limited [43].

Molecular targets of hydrogen peroxide

H_2O_2 is a mild oxidant and hence relatively inert to most biomolecules; nevertheless it is able to induce reversible, covalent modifications of cysteine thiolate residues located in active and allosteric sites of specific proteins resulting in alterations on their activity and function. Any protein containing a deprotonated cysteine residue is susceptible to be oxidized by H_2O_2 [44]; thus the sensitivity of the protein to oxidation depends on the ionization constant (pKa) and the local environment of the cysteine residue. Because the pKa of the sulfhydril group of most cysteines residues is around 8.5, they are protonated at physiological pH (Cys–SH), and so, inert to H_2O_2 oxidation. However, there are certain proteins which exhibit a lower pKa (5,6) and thus under physiological conditions they contain cysteine thiolate anions prone to react with H_2O_2 under second order kinetics. H_2O_2 is capable of oxidizing those cysteine residues via the formation of an unstable intermediate cysteine sulfenic acid (R–S–OH), and produce disulfides (R–S–S–R) [45,46]. Different kinds of disulfide bonds can occur depending on whether they are produced between cysteines within the same protein (intramolecular disulfide bond [47]) or between cysteines located in two different molecules producing a homo- or hetero-dimer (intermolecular disulfide bond [48]). In addition, disulfides can also form a mixed-disulfide between glutathione and the thiol of another protein (S-glutathionylation), or with amides to form sulfenyl amide (–SN–) [49]. Protein thiols can undergo further two-electron oxidations by H_2O_2 to form sulfinic (R–SO_2H) or sulfonic acid (R–SO_3H). Once a cysteine thiol has been oxidized, it needs to be reduced back if the signal has to be ended, and the cells are provided by different enzymatic and non-enzymatic systems responsible for this process. Disulfides and sulfenic groups can be reduced either by thioredoxins (TRXs) and peroxiredoxins (PRXs), while the mixed-disulfide reduction is driven by glutaredoxins (GRXs) [50]. Sulfinic acid groups can be reduced to sulfenic by the sulfiredoxins (SRXs) a family of ATP-dependent enzymes [51], and overoxidation to sulfonic acid is considered to be biologically irreversible.

Different proteins are capable to be modified by H_2O_2 including phosphatases, transcription factors, ion channels, antioxidant and metabolic enzymes, structural proteins and protein kinases among others [19]. In the next section, we focus on the interaction between ROS and protein kinases that are involved in the control of the vascular function.

Protein kinases constitute a highly diverse group of enzymes that alter the function of target proteins by catalyzing the phosphorylation of tyrosine, threonine, and/or serine residues [52]. A significant number of them are sensitive to redox signaling as they bear redox-sensitive cysteines, either in the primary kinases themselves or in upstream regulatory proteins. Some serine/theonine protein kinases are modified by a direct redox modification of susceptible cysteines. For example protein kinase C (PKC) contains a cysteine rich domain susceptible to oxidation [53], or the nonreceptor tyrosine kinase Src in which endogenous H_2O_2 oxidizes Cys-245 and Cys-487 in the kinase domain resulting in the activation of the protein [54], whereas tyrosine kinases are mainly activated in an indirect way, because of the oxidative inactivation of the protein tyrosine phosphatases (PTP) which control their phosphorylated state. All PTPs contain cysteine residues in their catalytic domains that are essential for their catalytic activity and exist as a thiolate [55,56]. This is frequently the mechanism of the ROS-mediated signal for an important group of protein kinases, widely involved in cell signaling, the mitogen-activated protein kinases (MAPK).

Table 1
Redox-induced effects on the vascular endothelium by MAPK.

MAPK	*Effect of thiol modification*	*Effect on the endothelium*	*References*
Erk1/2	*Activation*	*Growth and proliferation*	[59,60]
	Activation	*Vasodilation*	[61]
		Barrier dysfunction	[62]
	Activation	*Actin cytoskeleton reorganization*	[63,64]
p38 MAPK	*Activation*	*Vasodilation*	[65]
	Activation	*Actin cytoskeleton reorganization*	[63,66]
	Activation	*Increase endothelial permeability*	[67–69]
JNK	*Activation*	*Apoptosis*	[70–72]
ERK5	*Activation*	*Inhibit endothelial apoptosis*	[73]

MAPKs are key components of signaling pathways triggered by G-protein-coupled receptors, tyrosine kinase receptors, integrins and cytokines. They are a large family of serine/theonine kinases that requires tyrosine and threonine phosphorylation in the loop for activation [57]. They consist of four families of proteins: the extracellular signal regulated kinase (Erk1/2), p38 MAPK, jun N-terminal kinase (JNK) and the extracellular signal-regulated kinase 5 (ERK5), all of them reported as targets of H_2O_2. The ERK cascade is principally involved in proliferation, differentiation, growth and cell survival, JNK in apoptosis/inflammation and p38 MAPK in cell motility and inflammatory responses [58]. Thus the panoply of consequences derived from their redox regulation is quite ample.

In Table 1 we summarize the findings regarding the activation of MAPK by hydrogen peroxide and their role in vascular endothelial function.

H_2O_2 regulation of endothelial function

In vascular endothelial cells, ROS gained attention as important second messengers by regulating the activity of signaling proteins, enzymes and ion channels in endothelial cells. H_2O_2 modulates different aspects of endothelial cell function, including endothelial cell growth and proliferation, survival, endothelium-dependent vasorelaxation, cytoskeletal reorganization, inflammatory responses and endothelium-regulated vascular remodeling, among others [11]. Whereas a modest increase and a tight controlled regulation of H_2O_2 is essential for the maintenance of vascular homeostasis, an aberrant redox signaling, usually induced by an excessive production of ROS and/or by decreases in antioxidant activity, may contribute to an alteration in vascular function and lead to vascular disease [74,75].

We now discuss two situations where hydrogen peroxide exerts a profound influence on endothelial cells.

Cell growth, proliferation and angiogenesis

Endothelial cells growth and survival are dependent on several factors coupled to the intracellular production of $O_2^{\bullet-}$ and H_2O_2 [76]. For example, the growth regulating p90RSK protein [59] and the early growth factor 1 (Egf1) [77] are activated in endothelial cells by a redox-dependent activation of Erk1/2 MAPK by H_2O_2. Moreover, several studies have demonstrated that ROS mediate numerous

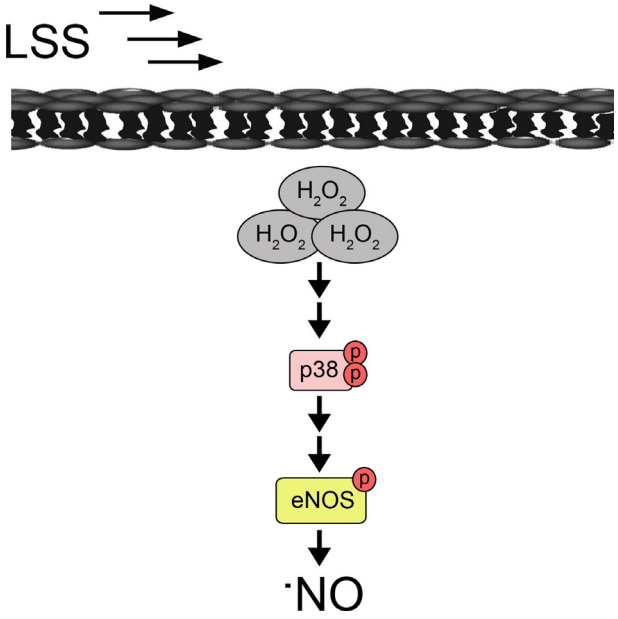

Fig 3. Laminar shear stress regulation of vascular tone.Hydrogen peroxide activation of p38 MAPK is a fundamental mechanism for laminar shear stress-mediated endothelium vasodilation.

angiogenic effects including migration, proliferation and tube formation, through a tight regulation between H_2O_2 and the key angiogenic growth factor VEGF [78]. On one side, H_2O_2 upregulates VEGF mRNA and protein expression and VEGF-induced VEGFR2 activation [59,79,80], inducing angiogenic-related responses. However, VEGF is also able to activate one of the main sources of ROS in vascular endothelial cells, NADPH oxidase [81,82].

It is important to note that these beneficial effects on the vasculature are only produced by physiological concentrations of H_2O_2 where endothelial cell growth and angiogenesis are necessary, as in repairing ischemia damage [83]. However, supraphysiological levels of H_2O_2 impair proliferation and/or decrease viability [84,85] or could even induce hypertrophy when diffusing to the smooth muscle [86].

Regulation of vascular tone and vascular relaxation

The effects of ROS on vascular tone are not uniform since they depend on the specific ROS molecule, its concentration, and the vascular bed that is affected among other factors [87]. In general, $O_2^{\bullet-}$ favors vasoconstriction because it reduces the bioavailability of nitric oxide ($NO^{\bullet}$) by reacting with it, and by generation of peroxynitrite [88,89]. In contrast, H_2O_2 induces vasodilation in different vascular beds, such as mesenteric [90,91], coronary [92,93] or pulmonary arteries [94]. The increment of H_2O_2 in vascular segments of transgenic mice with endothelial-specific NOX4 overexpression, lead to an increased vasodilation and reduced basal blood pressure [95]. H_2O_2 generation contributes to the physiological regulation of the vascular tone in different ways. It was found to be an endothelium-derived hyperpolarizing factor [96,97] or an activator of the potassium channel [98], but its vasorelaxing effect has been closely related to nitric oxide production. Indeed, H_2O_2 leads to the stimulation of eNOS and the subsequent production of nitric oxide via the activation of different signaling pathways such as PI3K/Akt [61,99] and Erk1/2 [61]. Furthermore, we have recently described the involvement of H_2O_2 in eNOS activation that may contribute to the protective role of laminar shear stress (LSS) in the vascular endothelium. We proposed a model in which LSS promotes the formation of signaling levels of H_2O_2, which in turn activate p38 MAPK and eNOS, increasing NO. synthesis and protection of endothelial function [65] (Fig. 3). Moreover, H_2O_2 has been described not only as capable of activating eNOS, but also for upregulating its expression [100]. A major regulator of vasodilation in the vasculature is the protein kinase PKG1α [101]. PKG1α is also sensitive to oxidation by H_2O_2 through the formation of a disulfide bond [102], accounting for the activation of the protein, and the related increased vasodilation independently of cGMP levels [103].

Conclusions

Hydrogen peroxide acts as a signaling second messenger in the vasculature. Its targets in the cardiovascular system are diverse, and include different protein kinases, which convey a wide array of effects to the endothelium. Although increased H_2O_2 might result in an alteration of vascular reactivity and lead to toxicity and the development of vascular disease, signaling levels of H_2O_2 play a key role in vascular function and homeostasis.

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