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Review article

Hydrogen peroxide is an endothelium-derived hyperpolarizing factor in animals and humans

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Abstract

The endothelium plays an important role in maintaining vascular homeostasis by synthesizing and releasing several vasodilating substances, including vasodilator prostaglandins, nitric oxide (NO), and endothelium-derived hyperpolarizing factor (EDHF). Since the first report for the existence of EDHF, several substances/mechanisms have been proposed for the nature of EDHF, including epoxyeicosatrienoic acids (metabolites of arachidonic P450 epoxygenase pathway), K ions, and electrical communications through myoendothelial gap junctions. We have recently demonstrated that endothelium-derived hydrogen peroxide (H_2O_2) is an EDHF in mouse and human mesenteric arteries and in porcine coronary microvessels. For the synthesis of H_2O_2 as an EDHF, endothelial Cu,Zn-superoxide dismutase plays an important role in mesenteric arteries of mice and humans. We also have demonstrated that EDHF-mediated responses are attenuated by several arteriosclerotic risk factors, including diabetes mellitus and hyperlipidemia and their combination in particular. Recent studies have indicated that endothelium-derived H_2O_2 plays an important protective role in coronary autoregulation and myocardial ischemia/reperfusion injury in vivo. Indeed, our H_2O_2/EDHF theory demonstrates that endothelium-derived H_2O_2, another reactive oxygen species in addition to NO, plays an important role as a redox signaling molecule to cause vasodilatation as well as cardioprotection. In this review, we summarize our knowledge on H_2O_2/EDHF regarding its identification, mechanisms of synthesis, and clinical implications.

Keywords: Endothelium; Endothelium-derived hyperpolarizing factor; Membrane potential; Hydrogen peroxide

1. Introduction

The endothelium synthesizes and releases several vasodilator substances, including vasodilator prostaglandins, nitric oxide (NO), and endothelium-derived hyperpolarizing factor (EDHF) [1,2]. Although the nature of EDHF has not been fully elucidated, different EDHFs could exist depending on species, blood vessels, and the size of blood vessels with different hyperpolarizing mechanisms involved [1,2]. Since the first report for the existence of EDHF [3,4], several candidates have been proposed for the nature of EDHF. Currently, the major candidates for EDHF include epoxyeicosatrienoic acids (EETs), metabolites of arachidonic P450 epoxygenase pathway [5,6], K ions [7,8], and electrical communication through myoendothelial gap junctions [9,10] (Fig. 1). We have demonstrated that endothelium-derived hydrogen peroxide (H_2O_2) is an EDHF in mouse [11] and human [12] mesenteric arteries and in porcine [13] and canine [14] coronary microvessels (Fig. 1). Although not universally accepted, other investigators also have reported that H_2O_2 may be an EDHF in the human coronary microvessels [15] and piglet pial arterioles [16]. We also have recently demonstrated that endothelial Cu,Zn-superoxide dismutase (SOD) plays an important role in the synthesis of H_2O_2 as an EDHF synthase in mouse [17] and human [18] mesenteric arteries. In this review, we will summarize the latest knowledge on our H_2O_2/EDHF theory, in terms of the identification, mechanisms of synthesis and clinical implications.

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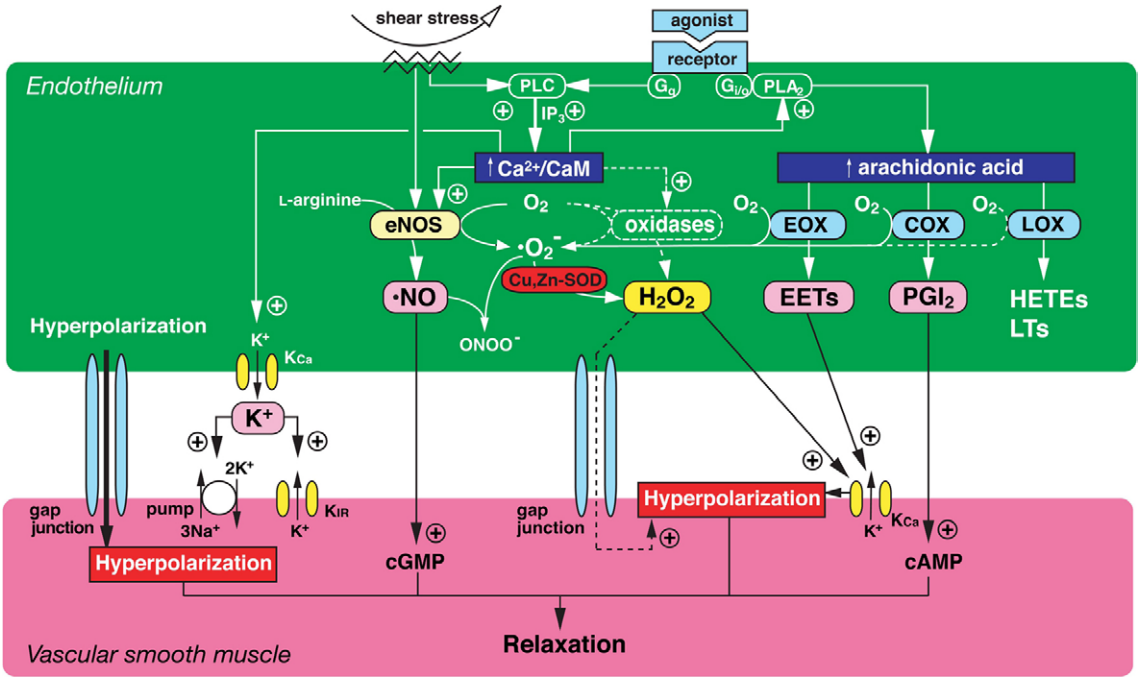

Fig. 1. Hypothesis on the nature of EDHF. Agonist stimulation and shear stress activate calcium–calmodulin complex and eNOS to produce NO, and also activate phospholipase A_2 to release arachidonic acid. NO activates soluble guanylate cyclase, produces cGMP, and relaxes vascular smooth muscle. Cyclooxygenase (COX) produces prostacyclin (PGI_2) from arachidonic acid and PGI_2 relaxes vascular smooth muscle in a cAMP-dependent manner. EDHF hyperpolarizes vascular smooth muscle by opening K channels and then elicits vasodilatation. Major candidates for the nature of EDHF include (1) epoxyeicosatrienoic acids (EETs), metabolites of arachidonic P450 epoxygenase pathway, (2) K ions released from the endothelium through endothelial K_{Ca} channels that activates Na,K-ATPase of vascular smooth muscle, and (3) electrical communication through myoendothelial gap junctions. We also have identified that (4) endothelium-derived H_2O_2 is an EDHF, for which eNOS is an important source.

2. History

It was known that acetylcholine induces hyperpolarization of vascular smooth muscle of rabbit mesenteric arteries [19] and that those hyperpolarizations are achieved in an endothelium-dependent manner [20]. In 1988, Feletou and Vanhoutte [3] and Chen et al. [4] independently demonstrated that a diffusible substance released by the endothelium causes hyperpolarization of underlying vascular smooth muscle, thus proposing the existence of EDHF [3,4].

2.1. Nature of EDHF

NO mediates vascular relaxation of relatively large, conduit arteries (i.e. aorta and epicardial coronary arteries), while EDHF plays an important role in modulating vascular tone in small, resistance arteries in vitro [21,22] and in human forearm microcirculation in vivo [23]. EDHF causes vascular relaxation by opening K channels and then hyperpolarizes membrane of vascular smooth muscle [1,2,22]. EDHF is synthesized not only upon stimulation by agonists but also by shear stress [24] and its synthesis and release are stimulated by increase in intracellular calcium in the endothelium [2,25], although calcium-independent endothelial cell hyperpolarization has also been reported [26]. Although NO and vasodilator prostaglandins elicit hyperpolarization of underlying vascular smooth muscle and NO may activate BK_{Ca} channels in some blood vessels [27], those responses to NO and vasodilator prostaglandins are largely inhibited by the inhibition of ATP-sensitive potassium (K_{ATP}) channels [2]. Importantly, substantial endothelium-dependent hyperpolarization exists even after the blockade of the synthesis of NO and vasodilator prostaglandins [2]. Thus, EDHF is apparently different from vasodilator prostaglandins or NO, and EDHF-mediated responses are classically defined as the endothelium-dependent responses (relaxations and hyperpolarizations) after the blockade of the synthesis of vasodilator prostaglandins and NO [2,25].

2.2. Vasodilating effect of reactive oxygen species (ROS)

Both NO- and EDHF-mediated responses are attenuated by various atherosclerotic risk factors [1,28], and the treatment of those risk factors improve both NO- and EDHF-mediated responses [1,29]. In various pathological situations, the production of ROS is increased while NO-mediated relaxations are attenuated. EDHF-mediated relaxations are temporarily enhanced to compensate the reduced NO-mediated relaxations, however, the EDHF-mediated responses also are subsequently reduced during the pathological process [1]. The endothelial synthesis of NO via eNOS activation is calcium/calmodulin-dependent and a similar requirement for calcium/calmodulin has been described for the EDHF-mediated response in the canine coronary artery [30]. These lines of evidence led us to hypothesize that EDHF is a non-NO vasodilator substance (possibly ROS) mainly derived from endothelial NO synthase (eNOS) [11].