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Review Article

Divergent roles of endothelial nitric oxide synthases system in maintaining cardiovascular homeostasis

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ABSTRACT

Accumulating evidence has demonstrated the importance of reactive oxygen species (ROS) as an essential second messenger in health and disease. Endothelial dysfunction is the hallmark of atherosclerotic cardiovascular diseases, in which pathological levels of ROS are substantially involved. The endothelium plays a crucial role in modulating tone of underlying vascular smooth muscle by synthesizing and releasing nitric oxide (NO) and endothelium-dependent hyperpolarization (EDH) factors in a distinct vessel size-dependent manner through the diverse roles of the endothelial NO synthases (NOSs) system. Endothelium-derived hydrogen peroxide (H_2O_2) is a physiological signaling molecule serving as one of the major EDH factors especially in microcirculations and has gained increasing attention in view of its emerging relevance for cardiovascular homeostasis. In the clinical settings, it has been reported that antioxidant supplements are unexpectedly ineffective to prevent cardiovascular events. These lines of evidence indicate the potential importance of the physiological balance between NO and H_2O_2/EDH through the diverse functions of endothelial NOSs system in maintaining cardiovascular homeostasis. A better understanding of cardiovascular redox signaling is certainly needed to develop novel therapeutic strategies in cardiovascular medicine. In this review, we will briefly summarize the current knowledge on the emerging regulatory roles of redox signaling pathways in cardiovascular homeostasis, with particular focus on the two endothelial NOSs-derived mediators, NO and H_2O_2/EDH.

1. Introduction

Reactive oxygen species (ROS) have been considered primarily harmful because of their highly-damaging entity to cells and tissues and pathological implications in various diseased states in humans [1,2]. The detrimental roles of ROS have been well-documented in a wide range of cardiovascular diseases in general, including atherosclerosis, hypertension, heart failure, cardiomyopathy, and coronary artery disease in particular, where endothelial dysfunction is also substantially involved in the pathophysiology [3]. However, accumulating evidence has provided firm foundations for a paradigm shift on the roles of ROS from pathological detriments to crucial physiological signaling molecules [4,5]. Thus, ROS have been re-evaluated as a physiological second messenger in light of recent advances in the better comprehension of their diverse regulatory roles in health and disease [6,7].

Endothelial dysfunction is the hallmark and potential predictor for atherosclerotic cardiovascular diseases and is also noted in patients with metabolic disorders, where prior exposure to various risk factors, such as diabetes mellitus, hypertension, and hypercholesterolemia, causes endothelial dysfunction, leading to the initial step toward atherosclerotic cardiovascular diseases [8]. A typical feature of endothelial dysfunction is reduced production of endothelium-derived relaxing factors, including vasodilator prostaglandins (PGs), nitric oxide (NO), and endothelium-dependent hyperpolarization (EDH) factors (Fig. 1). Although the nature of EDH factors varies depending on species and vascular beds examined, endothelium-derived hydrogen peroxide (H_2O_2) is one of the major EDH factors in various vascular beds in animals and humans and has gained increasing attention in view of its emerging relevance for cardiovascular homeostasis [9]. Importantly, the endothelium synthesizes and releases NO and H_2O_2/EDH to regulate vascular tone in a distinct vessel size-dependent manner through the diverse roles of the NO synthases (NOSs) system; NOS mainly serves as a NO-generating system to elicit soluble guanylate cyclase (sGC)-cyclic guanosine monophosphate (cGMP)-mediated relaxations in large conduit vessels and a superoxide-gener-

Abbreviations: AMPK, AMP-activated protein kinase; cGMP, cyclic guanosine monophosphate; EDH, endothelium-dependent hyperpolarization; H_2O_2, hydrogen peroxide; NO, nitric oxide; NOS, nitric oxide synthase; PGs, prostaglandins; PKG, cGMP-dependent protein kinase; ROS, reactive oxygen species; SERCA, sarco/endoplasmic reticulum calcium ATPase; sGC, soluble guanylate cyclase; SOD, superoxide dismutase

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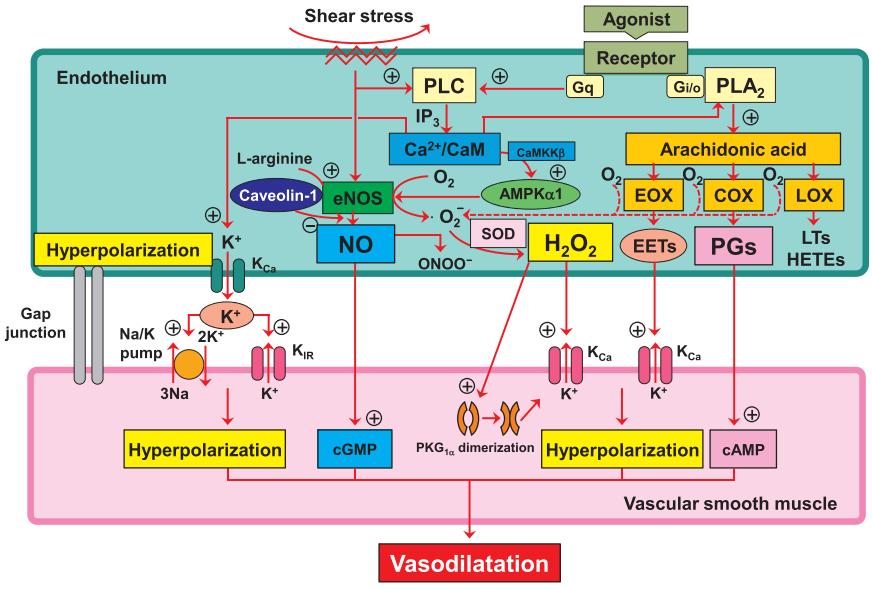

Fig. 1. Mechanisms for synthesis and action of endothelium-derived relaxing factors. In addition to vasodilator prostaglandins (PGs) and nitric oxide (NO), several candidates could act as endothelium-dependent hyperpolarizing (EDH) factor. PGs, NO, and EDH factor cause relaxations of underlying vascular smooth muscle through the mechanisms mediated by cyclic AMP (cAMP), cyclic GMP (cGMP) and hyperpolarization mediated by opening of Ca-activated K (KCa) channels, respectively. Other abbreviations: AMPKα1, α1-subunit of AMP-activated protein kinase; CaM, calmodulin; CaMKKβ, Ca^{2+}/CaM-dependent protein kinase β; COX, cyclooxygenase; EETs, epoxyeicosatrienoic acids; eNOS, endothelial NO synthase; EOX, epoxygenase; HETEs, hydroxyeicosatetraenoic acids; H_2O_2, hydrogen peroxide; IP_3, inositol trisphosphate; LOX, lipoxygenase; LTs, leukotrienes; $ONOO^-$, peroxynitrite; $PKG_{1\alpha}$, 1α-subunit of protein kinase G; PLA_2, phospholipase A_2; PLC, phospholipase C; SOD, superoxide dismutase.

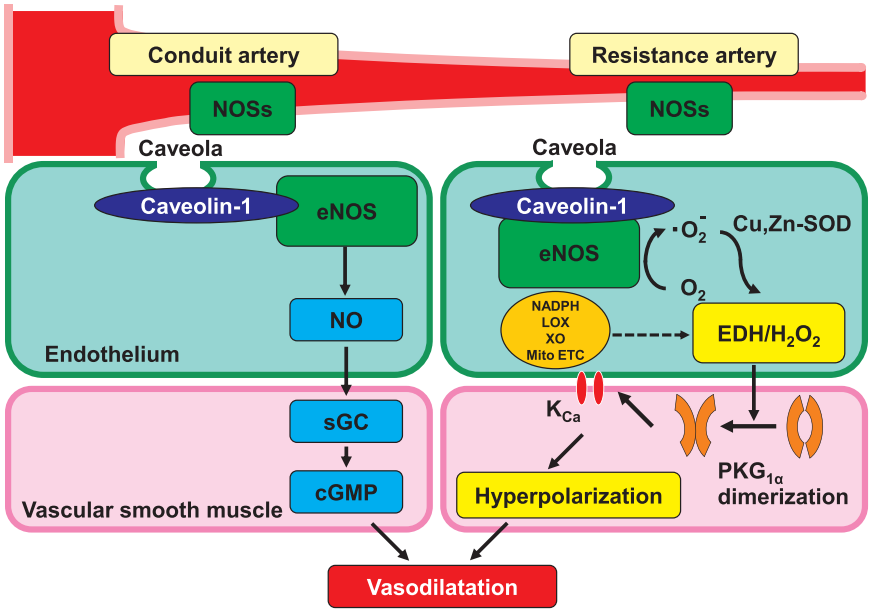

Fig. 2. Diverse roles of endothelial nitric oxide synthases system. In large conduit vessels, NO synthases (NOSs) mainly serve as a NO-generating system to cause vasodilatation through soluble guanylate cyclase (sGC)-cGMP pathway, while in small resistance vessels, they act as a superoxide-generating system to evoke EDH-mediated responses through H_2O_2-induced $PKG_{1\alpha}$ dimerization and subsequent activation of potassium channels, leading to hyperpolarization and vasodilatation. Other abbreviations: Cu, Zn-SOD, zinc-superoxide dismutase; KCa, calcium-activated potassium channel; LOX, lipoxygenase; Mito ETC, mitochondrial electron transport chain; NADPH, reduced nicotinamide adenine dinucleotide phosphate oxidase; $ONOO^-$, peroxynitrite; $PKG_{1\alpha}$, 1α-subunit of protein kinase G; XO, xanthine oxidase.

ating system to cause H_2O_2/EDH -mediated responses in small resistance vessels [10] (Fig. 2). In the clinical settings, it has been reported that chronic nitrate therapy could exert harmful effects in patients with ischemia heart disease [11,12] and that antioxidant supplements are unexpectedly ineffective to prevent cardiovascular events [13]. These lines of evidence suggest the potential importance of the physiological balance between NO and H_2O_2/EDH through the diverse functions of endothelial NOSs system in maintaining cardiovascular homeostasis.

Obviously, a growing number of recent publications and review articles in this field reflect that our scientific community craves for much better understanding of this complex but promising redox signaling systems and its clinical application for curing diseases associated with oxidative stress [5,14–18]. In this review, we will briefly summarize the current knowledge on the emerging regulatory roles of redox signaling pathways in cardiovascular homeostasis, with particular focus on the two endothelial NOSs-derived mediators, NO and H_2O_2/EDH.