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Significance of Nitric Oxide in Cardio Vascular Health

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ABSTRACT: Nitric oxide (NO) is a gaseous lipophilic free radical cellular messenger generated by three distinct isoforms of nitric oxide synthases (NOS), neuronal (nNOS), inducible (iNOS) and endothelial NOS (eNOS). NO plays an important role in the protection against the onset and progression of cardiovascular disease. Cardiovascular disease is associated with a number of different disorders including hypercholesterolaemia, hypertension and diabetes. The underlying pathology for most cardiovascular diseases is atherosclerosis, which is in turn associated with endothelial dysfunctional. The cardioprotective roles of NO include regulation of blood pressure and vascular tone, inhibition of platelet aggregation and leukocyte adhesion, and prevention smooth muscle cell proliferation. Reduced bioavailability of NO is thought to be one of the central factors common to cardiovascular disease, although it is unclear whether this is a cause of, or result of, endothelial dysfunction. Disturbances in NO bioavailability leads to a loss of the cardio protective actions and in some case may even increase disease progression.

KEYWORDS: nitric oxide, cardiovascular, health, significance, cardioprotective, disease, endothelial

I. INTRODUCTION

Nitric oxide is a soluble gas continuously synthesized by the endothelium. This substance has a wide range of biological properties that maintain vascular homeostasis, including modulation of vascular dilator tone, regulation of local cell growth, and protection of the vessel from injurious consequences of platelets and cells circulating in blood. A growing list of conditions, including those commonly associated as risk factors for atherosclerosis such as hypertension and hypercholesterolemia, are associated with diminished release of nitric oxide into the arterial wall either because of impaired synthesis[1,2] or excessive oxidative degradation. Diminished nitric oxide bioactivity may cause constriction of coronary arteries during exercise or during mental stress and contribute to provocation of myocardial ischemia in patients with coronary artery disease. Additionally, diminished nitric oxide bioactivity may facilitate vascular inflammation that could lead to oxidation of lipoproteins and foam cell formation, the precursor of the atherosclerotic plaque. Numerous therapies have been investigated to assess the possibility of reversing endothelial dysfunction by enhancing the release of nitric oxide from the endothelium, either through stimulation of nitric oxide synthesis or protection of nitric oxide from oxidative inactivation and conversion to toxic molecules such as peroxynitrite.[3,4]

Nitric oxide (NO) signalling has pleiotropic roles in biology and a crucial function in cardiovascular homeostasis. Tremendous knowledge has been accumulated on the mechanisms of the nitric oxide synthase (NOS)–NO pathway, but how this highly reactive, free radical gas signals to specific targets for precise regulation of cardiovascular function remains the focus of much intense research. There are updated paradigms on NOS regulation, NO interaction with reactive oxidant species in specific subcellular compartments, and downstream effects of NO in target cardiovascular tissues, while emphasizing the latest developments of molecular tools and biomarkers to modulate and monitor NO production and bioavailability.[5,6]

The importance of nitric oxide (NO) for normal cardiovascular regulation and health has been well established. However, the large majority of the focus and knowledge about NO has revolved around the endothelium and endothelial derived NO. Aside from its importance for blood flow and blood pressure via endothelium-dependent vasodilation, endothelial NO synthase (eNOS) has been shown to have numerous other vascular protective effects including, but not limited to, inhibition of platelet aggregation and adhesion, promotion of angiogenesis, anti-inflammation, and inhibition of the atherosclerotic process. In addition, eNOS has important cardiac effects. Thus, it is clear that impairments in eNOS-derived NO can have deleterious consequences and play a role in the disease process.[7,8] Although the aforementioned functions of eNOS cannot be overstated, the synthesis of NO via neuronal NOS (nNOS) may also be critical for cardiovascular regulation and health. Indeed, nNOS along with eNOS is constitutively expressed in mammalian cells, and an emerging body of research, mainly performed in animals, has

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indicated that nNOS may also be important for the regulation of vasomotor tone and blood pressure. However, much less is known about nNOS in humans.

Nitric oxide is a soluble gas with a half-life of ~6–30 s, continuously synthesized from the amino acid L-arginine in endothelial cells by the constitutive calcium-calmodulin-dependent enzyme nitric oxide synthase (1). This heme-containing oxygenase catalyzes a five-electron oxidation from one of the basic guanidino nitrogen atoms of L-arginine in the presence of multiple cofactors and oxygen. In their seminal experiment, Furchgott and Zawadzki (2) found that strips of rabbit aorta with intact endothelium relaxed in response to acetylcholine but constricted in response to this same agonist when the endothelium had been rubbed off. The substance responsible for the acetylcholine-stimulated relaxation was initially called endothelium-derived relaxant factor, and subsequently found to include nitric oxide (3)(4). It is now known that a variety of agonists[9,10] (e.g., acetylcholine, histamine, thrombin, serotonin, ADP, bradykinin, norepinephrine, substance P, and isoproterenol) can increase the synthesis and release of nitric oxide from the endothelium, although many of these same agonists (e.g., acetylcholine, serotonin, norepinephrine, and histamine) constrict vascular smooth muscle in the absence of endothelium. Vasoactive substances produced within the endothelium, such as bradykinin, may also stimulate nitric oxide release by autocrine and paracrine effects on endothelial B_2 kinin receptors (5). However, the principal physiologic stimulus for nitric oxide synthesis and release from the endothelium is likely the shear stress of blood flowing over the surface of the vessel by a nonreceptor-dependent mechanism (6)(7). Nitric oxide, released from the endothelium as a gas or attached to other molecules, stimulates soluble guanylyl cyclase, producing increased concentrations of cyclic GMP. Depending on the direction of nitric oxide release and the site of cyclic GMP activation, differing biological effects can be observed. For example, increased cyclic GMP in vascular smooth muscle cells underlying the endothelium activates GMP-dependent kinases[11,12] that decrease intracellular calcium, producing relaxation (8), whereas increased cyclic GMP in platelets by action of nitric oxide released into the blood vessel lumen decreases platelet activation and adhesion to the surface of the endothelium (9). Nitric oxide also regulates the cellular environment within the vessel wall by inhibiting the activity of growth factors released from cells within the vessel wall and from platelets on the endothelial surface (10). Nitric oxide has antiinflammatory properties by inhibiting the synthesis and expression of cytokines and cell adhesion molecules that attract inflammatory cells to the endothelial surface and facilitate their entrance into the vessel wall (11)(12). This effect of nitric oxide may be mediated by inhibition of the activation of an important nuclear transcription factor (nuclear factor κB) that binds to the promoter regions of genes that code for proinflammatory proteins (12). Nitric oxide also governs basal systemic, coronary, and pulmonary vascular tone by increased cyclic GMP in smooth muscle, by inhibition of a potent constrictor peptide, endothelin-1 (13), and by inhibition of the release of norepinephrine from sympathetic nerve terminals (14).

Thus, nitric oxide plays a pivotal role in regulating vessel wall homeostasis. Although the endothelium-dependent processes to be discussed involve a multitude of metabolic and gene transcriptional pathways, nitric oxide either directly or indirectly plays an important role in their regulation.[13]

II. DISCUSSION

NO is produced by nitric oxide synthase (NOS) enzymes, of which there are three main

isoforms: neuronal NOS (nNOS), endothelial NOS (eNOS), and inducible NOS (iNOS).14

Table 1 shows a comparison of these isoforms. The three NOS isoforms are encoded

on separate chromosomes by separate genes. They share homology in regions involved in cofactor binding (for example, FAD, FMN, and NADPH ribose and adenine binding sites), and have similar enzymatic mechanisms that involve electron transfer for oxidation of the terminal guanidino nitrogen of L-arginine. However, their expression patterns differ, as do the detailed regulations of their activity. nNOS is predominantly expressed in certain neurons and in skeletal muscle, whereas eNOS is predominantly expressed in endothelial cells. iNOS is expressed by macrophages and cells of macrophage/monocyte lineage. Despite their names, a variety of cell types express these isoforms, with many tissues expressing more than one isoform. Furthermore, the innervation and vasculature in all tissues have the potential to express nNOS and eNOS, while circulating blood elements may express iNOS.[14,15]

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Table 1
Characteristics of NOS Isoforms

Isoform	nNOS	iNOS	eNOS
Other names	NOS-1, NOSI, Type I NOS	NOS-2, NOSII, Type II NOS	NOS-3, NOSIII, Type III NOS
Human chromosomal location	12q24.2-12q24.3	17cen-q11.2	7q35–7q36
Human gene structure and size	29 exons	26 exons	26 exons
	locus region >200 kbp	37 kbp	21–22 kbp
Human monomer size (predominant form)	161 kDa	131 kDa	133 kDa
Splice variants	Yes	Yes	No
Typical site of expression	Neurons	Macrophages	Endothelial cells
Other major sites of expression	Smooth muscle	Smooth muscle	Smooth muscle
	Skeletal muscle	Liver	Platelets
Gene expression	Constitutive and inducible	Inducible	Constitutive and inducible
Ca^{2+} dependency	Ca^{2+}-dependent	Practically Ca^{2+}-independent	Ca^{2+}-dependent
Covalent modifications	Phosphorylation		Myristoylation
			Palmitoylation
			Phosphorylation
Protein–protein interactions	hsp90, caveolin, NOSIP		hsp90, caveolin
Subcellular localization	Neuromuscular junction	Soluble	Caveolae
	Soluble		
	Sarcoplasmic reticulum		

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Isoform	nNOS	iNOS	eNOS
Means of localization	N-terminal PDZ domain (for membrane association)	N/A	N-terminal myristoylation
NO production (range)	Moderate (nM to μM)	High (μM)	Low (pm to nM)

Both nNOS and eNOS are generally constitutively expressed; their activities are primarily regulated by intracellular Ca^{2+}/calmodulin levels. In contrast, iNOS expression is induced in

activated macrophages as an immune response. For enzymatic activity, NOS proteins must bind cofactors and dimerize.14 NOS proteins first bind to the cofactors FAD and FMN. The additions of L-arginine, BH_4 and heme allow the NOS protein to form dimers. eNOS and nNOS dimers formed this way are inactive, and depend on calmodulin binding stimulated by increases in intracellular calcium. In contrast, the iNOS dimers bind calcium/calmodulin and are active even at low (resting intracellular) concentrations of calcium. Thus, the main switch for activity for nNOS and eNOS is a transient increase in intracellular calcium concentration, whereas the main switch for iNOS is at the level of transcription.[16,17]

The DNA and protein sequences of the NOS isoforms are conserved between species, with nNOS, eNOS and iNOS sharing up to 96%, 93% and 80% amino acid sequence identity between mice and humans. Within each species, the NOS isoforms share about 51–59% amino acid sequence identity. Each isoform has notable structural features. The nNOS gene encodes a PDZ domain in exon 2 that is required for membrane association.15 Several nNOS splice variants lack exon 2, resulting in expression of cytoplasmic nNOS that lacks subcellular localization sequences.16,17 In endothelial cells, eNOS is localized to caveolae by N-terminal fatty acid modifications—myristoylation and palmitoylation,18–21 as well as interactions with heat shock protein hsp90 and caveolins.12,22 Caveolins (caveolin-1 in endothelial cells and caveolin-3 in cardiac muscle) bind to eNOS and inhibit its activity. eNOS is also regulated by phosphorylation at multiple sites, including serine 1179 and threonine 497.[18,19]

In addition to nNOS, eNOS, and iNOS, there is a constitutively active NOS isoform present in mitochondria, referred to as mtNOS.23,24 mtNOS is located in the inner mitochondrial membrane, and likely plays key roles in modulating mitochondrial respiration and mitochondrial transmembrane potential. However, whether mtNOS corresponds to one of the three known isoforms is not known.

III. RESULTS

The underlying pathology of most cardiovascular diseases (CVDs) such as coronary artery disease, high blood pressure, and stroke involves decreased cardiovascular contractility and anatomic alterations in cardiovascular structures. Nitric oxide (NO) regulates vascular tone and contractile function of myocardium and maintains blood vessel homeostasis. Interestingly, the effect of NO is like a double-edged sword in the body. Insufficient NO causes hypertension and atherosclerosis, while an overproduction of NO may foster inflammation and cause heart infarction and shock. In addition, growing evidences have shown that oxidative stress plays pivotal roles in the initiation and progression of CVDs. This chapter will discuss in detail the roles NO plays in the cardiovascular system under both physiological and pathological conditions. We will focus on: (1) the molecular mechanism of cardiovascular contraction, (2) NO/Ca2+-induced muscle relaxation, (3) NO-related structural change in blood vessels, and (4) redox balance in the cardiovascular system.[20,21]

Nitric oxide is produced by nearly every type of cell in the human body and one of the most important molecules for blood vessel health.It's a vasodilator, meaning it relaxes the inner muscles of your blood vessels, causing the vessels to widen. In this way, nitric oxide increases blood flow and lowers blood pressure.Supplements that increase nitric oxide in the body make up one of the most popular supplement categories today.These supplements don't contain nitric oxide itself. However, they contain compounds that your body can use to make nitric oxide and have been shown to provide many benefits for health and performance.[22]

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IV. CONCLUSIONS

Hypertension is a major risk factor for cardiovascular disease, and reduction of elevated blood pressure significantly reduces the risk of cardiovascular events. Endothelial dysfunction, which is characterized by impairment of nitric oxide (NO) bioavailability, is an important risk factor for both hypertension and cardiovascular disease and may represent a major link between the conditions. [23] Evidence suggests that NO plays a major role in regulating blood pressure and that impaired NO bioactivity is an important component of hypertension. Mice with disruption of the gene for endothelial NO synthase have elevated blood pressure levels compared with control animals, suggesting a genetic component to the link between impaired NO bioactivity and hypertension. Clinical studies have shown that patients with hypertension have a blunted arterial vasodilatory response to infusion of endothelium-dependent vasodilators and that inhibition of NO raises blood pressure.[24,25] Impaired NO bioactivity is also implicated in arterial stiffness, a major mechanism of systolic hypertension. Clarification of the mechanisms of impaired NO bioactivity in hypertension could have important implications for the treatment of hypertension.[26]

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