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Recent advances in the understanding of the role of nitric oxide in cardiovascular homeostasis

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Abstract

Nitric oxide synthases (NOS) are the enzymes responsible for nitric oxide (NO) generation. To date, 3 distinct NOS isoforms have been identified: neuronal NOS (NOS1), inducible NOS (NOS2), and endothelial NOS (NOS3). Biochemically, NOS consists of a flavin-containing reductase domain, a heme-containing oxygenase domain, and regulatory sites. NOS catalyse an overall 5-electron oxidation of one N^{ω}-atom of the guanidino group of L-arginine to form NO and L-citrulline. NO exerts a plethora of biological effects in the cardiovascular system. The basal formation of NO in mitochondria by a mitochondrial NOS seems to be one of the main regulators of cellular respiration, mitochondrial transmembrane potential, and transmembrane proton gradient. This review focuses on recent advances in the understanding of the role of enzyme and enzyme-independent NO formation, regulation of NO bioactivity, new aspects of NO on cardiac function and morphology, and the clinical impact and perspectives of these recent advances in our knowledge on NO-related pathways.

Abbreviations: ADMA, asymmetric dimethylarginine; ATP, adenosine triphosphate; BH_4, tetrahydrobiopterin; CAT-1, cation arginine transporter 1; cGMP, guanosine-3′5′-cyclic monophosphate; DDAH, dimethylarginine dimethylaminohydrolase; GTP, guanosine triphosphate; Hsp90, 90 kDa heat shock protein; HNO, nitroxyl; IL, interleukin; IP3, phosphatidylinositol triphosphate; INF, interferon; NADPH, nicotinamide adenine dinucleotide phosphate, reduced form; N_2O_3, dinitrogen trioxide; NO, nitric oxide; NO^-, nitroxyl anion; NO^+, nitrosonium ion; NO_2, nitrogen dioxide; NO_2^-, nitrite; NOHb, nitrosylhemoglobin; NOSIP, eNOS-interacting protein; NOSTRIN, eNOS traffic inducer; NOS, nitric oxide synthase; NOS1, neuronal nitric oxide synthase (nNOS); NOS2, inducible nitric oxide synthase (iNOS); NOS3, endothelial nitric oxide synthase (eNOS); O_2^-, superoxide anion; O_2, oxygen; $ONOO^-$, peroxynitrite; PK, protein kinase; RSNO, *S*-nitrosothiol species; RNNO, *N*-nitrosamine species; ROS, reactive oxygen species; RBC, red blood cell; sGC, soluble guanylyl cyclase; SNOAlb, *S*-nitrosoalbumin; SNOHb, *S*-nitrosohemoglobin; TNF, tumor necrosis factor.

Contents

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1. Introduction

Nitric oxide (NO) is a pivotal regulator of cardiovascular homeostasis. Its generation by nitric oxide synthases (NOS) has been recognised and extensively investigated for nearly a quarter of century. It is clear that the generation and actions of NO under physiological and pathophysiological conditions are exquisitely regulated and extend to almost every cell type and function within the circulation. The last 5 or 6 years have witnessed huge advances in our understanding of NO generation and actions. NO is derived not only from NOS isoforms but also from NOS-independent sources. The localisation of NO within cells and within the circulation is being extensively investigated. The regulation of the biological activity of NO after its formation and the chemistry of NO and its derivatives underpin a detailed understanding of the physiological and pathophysiological roles of NO in a number of important cardiovascular tissues. Most notably in this regard, the myocardial actions of NO have received a great deal of attention. Here, we provide an update that summarises the most significant advances in NO biochemistry and physiology during the last few years that contribute to our increasing understanding of its multidimensional roles in cardiovascular homeostasis. We conclude by placing this new information within the clinical context and provide some perspectives on therapeutic applications.

2. Regulation of nitric oxide synthase activity

Three isoforms of NOS have been cloned (Balligand & Cannon, 1997; Alderton et al., 2001): the neuronal NOS (nNOS or NOS1, 150 kDa protein, encoded by the *NOS1* gene), the inducible NOS (iNOS or NOS2, 130 kDa protein, encoded by the *NOS2* gene), which is the only calcium-independent isoform, and finally, the endothelial NOS (eNOS or NOS3, 133 kDa protein, encoded by the *NOS3* gene). All isoforms are expressed in cardiovascular tissues. Constitutive NOS isoforms (NOS1 and NOS3) are specifically and highly regulated at both transcriptional (expression and abundance) and post-translational (activity and function) levels, whereas NOS2 is almost exclusively regulated transcriptionally. Positive and negative regulators of both the protein expression and activity of NOS isoforms that are largely or exclusively restricted to cardiovascular