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Review Article

Nitric oxide functions in the heart

Abstract

Nitric oxide (NO) is an important organizer of the cardiovascular function and is an important mechanism in hampering the pathogenesis of the diseased heart. The scenario of bioavailable NO in the myocardium is complicated: 1) NO obtain from both endogenous and exogenous NO synthases (NOSs) and the number of NO from exogenous sources varies considerably. 2) NOSs are located at separated regions of cardiac cells and are organized by varied ways under stress.3) NO arranges various target proteins via different ways of post-transcriptional modification which are soluble guanylate cyclase [sGC]/cyclic guanosine monophosphate [cGMP]/protein kinase G [PKG]-dependent phosphorylation, S-nitrosylation, and trans-nitrosylation. 4) the downgradient stabilizers of NO differ from proteins and enzymes in the mitochondria and membrane.5) NOS generates several radicals in addition to that NO (varied NO-associated yields) and stimulates redox responses. But, NOS inhibits cardiac oxidases to diminish the sources of oxidative stress in diseased hearts. Recent consensus indicates the importance of nNOS protein in cardiac protection under pathological stress and NO-dependent mechanisms are better understood in healthy and diseased hearts.

Introduction

Nitric oxide (NO) is a primary matter that plays important roles in maintaining cardiovascular functions in humans [1–5]. The NO that argues positions in the myocardium can be obtained via exogenous matters or is generated from the endogenous NO synthases and alertable NOS by inflammatory cytokines following infection [4–6]. The impacts of NO on myocardial functions and the roles for NOS in diseased hearts has improved in the last times. Overall approaches have been assumed to succeed this outcome, containing manipulation of stabilizers of to supplementation of NO mimetics, and precise detection of plasma and tissue NO [4,5,7,8]. Even so, the practical arguments of NO and its regulators in therapeutic strategies in cardiovascular diseases hamper because of the compound nature of NO and the array of downstream signaling cascades and stabilizations in the myocardium.

Resource of NO and effect mechanisms

It is affirmed that NO is varied from the standard L-arginine–NOS–NO way. Actually, NO that performs functions in the myocardium may also be obtained from the other source of NO. Nitrate (NO_3^-) in many types of green vegetables [9–11], is taken up into the plasma to become a safe reservoir and the decisive pioneer of NO. Nitrate from this source is taken on by the salivary , is secreted in the intensified form in the saliva, and is right after diminished to more active nitrite (NO_2^-) in the oral cavity by nitrate reductases of commensal bacteria. Nitrite is decreased to NO in the stomach and is sucked up into the plasma in the gastrointestinal system. Many proteins are known to be contained in the NO metabolite cycle and nitrite's reduction to NO, including xanthine oxidase [12,13], deoxyhemoglobin and deoxymyoglobin [14–16], neuroglobin [17], respiratory chain enzymes [18], cytochrome P450 [19], aldehyde oxidase [20], carbonic anhydrase (21) and NO synthase [22,23].Indepth, up to 25% of nitrate re-uptake by the salivary and generates NO in the circulation; the rest of the nitrate is secreted in the urine. The number of NO from exogenous can be as high as the number that is generated from NOS in the tissues, indicating the importance of this pathway in supplementing local NO in the tissue. The effectiveness, food derived functional NO is oxygen independent [10,11]. Accordingly, NO from this source becomes more important in ischemic conditions, like myocardial infarction. NO can undergo an oxidative process via nNOS and generate decisive nitrate, which can be diminished back to nitrite and NO by nitrate reductases, such as xanthine oxidoreductase or aldehyde oxidase [10,11]. Consequently, there is a fixed of NO metabolites, and NO that maintains exogenous NO in the body. The respective additives of the endogenous versus exogenous NO to intracellular signaling and function in hearts in vivo remain to reveal. Some tissues are the active sites for NO production from constitutive NOS. Lately, it has demonstrated that muscle is a nitrate store up that gains plasma NO because of the wideness of the tissue in the body [24]. nNOS in the skeletal muscle promotes to the supply because it is the isoform in the skeletal muscle [25]. But, the NO from the specific sources that promote to the bioavailable NO in the myocardium. eNOS is the main isoform of NOS that plays significant roles in NO regulation of functions in the majority of tissues, including the heart [4,5,7,8]. In

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the myocyte, eNOS is located in the plasma membrane, golgi apparatus, nucleus, and mitochondria [8,26]. eNOS exhibits the highest activity at the membrane, followed by outer layers of the cis-Golgi and little activity in the cytosol, nucleus, and mitochondria [26,27]; therefore, localization is the primary determinant of eNOS activity for specific biological functions. Conversely, mislocalization of eNOS has been demonstrated to diminish its capacity to produce NO in cells [26–28]. The last consensus is that nNOS is the isoform that plays the major role in cardiac tissue because nNOS is showed in all heart [7,8]. As such, nNOS is well placed to fill primary roles in modifying sympathetic and parasympathetic tones.nNOS is localized in the sarcoplasmic reticulum (SR) [6], and is contained in the Ca2+ handling processes of cardiac excitation-contraction coupling in the myocardium [7,8]. Lately, A study has demonstrated that nNOS is upregulated in the myocardium from the disease progression [29-32], and facilitates lusitropy through myofilament Ca2+ desensitization [32,33]. Until now, most of the responses of nNOS attributed nNOSα or nNOSμ [7,8]. But, the existence of many splice variants of nNOS (nNOSβ, nNOSγ, and nNOS2) suggests that lie variants of nNOS may be contained in generating NO and organizing a contractile function in the heart. Recently, we have presented new evidence to demonstrate that nNOSβ, which does not have the PDZ domain, is stated in the cardiac myocytes from the hearts of rats [34]. These results indicate that nNOSβ may play the major roles in myofilament. It has been reported in skeletal muscle that nNOSβ is stated in the Golgi apparatus and mediates myofilament regulation during exercise [25]. An overall understanding of nNOS and its tie various in the organelles and their roles in cardiac function in the hearts. Remarkable, the co-existence of eNOS and, nNOS and their many ties in the myocardium [7,8,35]. A conflictive leaning presents this in protein activities of eNOS and nNOS in the frailty heart; namely, eNOS expression is diminished considerably, while nNOS activity is enhanced [30–32,36]. Otherwise, nNOS to protect the myocardium from Ca2+ oxidative stress [7,31,37], and both eNOS and nNOS influence intracellular Ca2+ in the cells, and eNOS enhanced Ca2+ transients in myocytes in response to increased preload [38]. Contrary, nNOS induced spontaneous Ca2+ [39]. Spatial redistribution of NOSs is related to both the changes of activity and the removal of the primary targets. Virtually, the nNOS may be useful in protection its business to apply for myocardial protection.

NO synthase

Many mechanisms correlator the impacts of nitric oxide synthase. It approves that soluble guanylate cyclase (sGC)/ cyclic guanosine monophosphate (cGMP) are the primary mechanisms that intercede the effects of NO in the body. The previous mechanism contains in post-translational modification of thiol in proteins by NO [40,41]. Protein-protein transfer of NO is known to present the most important mechanisms of NO [42]. In this process, the SNO proteins are referred to as nitrosyl asses. Trans- S-nitrosylation possesses advantages for efficient interactions between proteins [43]. Furthermore, trans-nitrosylation is important when NO bioavailability is limited in an oxidative and nitrosative stress environment, such as during ischemia reperfusion. S-nitrosylation can be ceased by the action of nitrosylates, with NADH and NADPH serving as electron donors to regenerate glutathione and thioredoxin [44,45]. Many types of proteins are targeted by NO e.g. inhibition of protein phosphatase 2A/ protein phosphatase one by NO causes protein kinase A (PKA) and phospholamban (PLN) [46], while sGC activation by NO in the myocardium of rats [32]. Contrary, phosphodiesterase 5 (PDE5) reactivation by NO system limits cytosolic cGMP, a negative feedback mechanism of NO regulation of cGMP in cardiac myocytes [47]. Additionally, by targeting cardiac oxidases, such as xanthine oxidoreductase [48], NADPH oxidase [49,50], and mitochondrial reactive oxygen species (ROS) production [51], nNOS-derived from NO controls in the myocardium. Cysteine residues are the targets of ROS to cause S-glutathionylation in the proteins [52,53]; thus, S-nitrosylation by NO may block cysteine residues from irreversible oxidation under the conditions. Eventually, post-transcriptional terms downstream of NO change the proteins, altering their activity, and function, as well as, nNOS has been showed to generate H2O2 in the endothelium of arteries, for example, the aorta, and H2O2 mediates endothelium-dependent vascular relaxation (54,55). Contrary, blight of endothelial has been demonstrated to worsen endothelial function in some diseases [56-58], likewise, both eNOS and nNOS promote to acetylcholine stimulation of vasodilatation [55], by regulating protein kinases and phosphatases [59–61]. Conversely, uncoupling of eNOS and nNOS [48,62–64], results in the production of superoxide (O2 -) in return for NO; eNOS and nNOS occur the oxidative stress for pathological progression in the heart. nNOS performs its cardiac protection via the ion channels, modulating abnormal Ca2+ homeostasis, and mitochondrial function for the pathological process [7,8]. nNOS organizes ion channels and Ca2+-handling proteins. Specially, nNOS has permanently been demonstrated to diminish Ca2+ influx via the L-type Ca2+ channel (LTCC) [65]. In support of this, nNOS enhances the vulnerability of the LTCC for Ca2+-dependent inactivation in hypertension [66] where intracellular Ca2+ transient is increased secondary to nNOS-dependent myofilament Ca2+ desensitization (34). Variation of the LTCC by nNOS may prohibit extreme intracellular Ca2+ in myocytes under pathological situations. The ryanodine receptor (RyR) by nNOS has been contained in diminishing diastolic Ca2+ leak [67], increasing RyR open probability, and growing contraction in cardiac myocytes [74]. Thus, nNOS protects against arrhythmogenesis by modulating Ca2+ transients [68-70].Besides, nNOS activity at the plasma membrane causes more significant Na+ influx via voltage-gated sodium channels via S-nitrosylation and increases the susceptibility of the myocardium for long QT and arrhythmias (34). Potassium channels are also potential targets of nNOS through S-nitrosylation and/or cGMP/PKG-dependent phosphorylation [71–73], which may play significant roles in the formation of cardiac function in hearts. NNOS-derived NO can cause S-nitrosylation of the SR calcium ATPase (SERCA) both under basal conditions [70,74]. Inhibition of nNOS decreases S-nitrosylation of SERCA at baseline level, and this is related to reduced Ca2+ uptake in the SR and decreased relaxation [74].

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But, the functional important of this formation under disease situations survives to be detected. These results consider that the modes of post-transcriptional modification that underlie the specific impacts of nNOS are excessively dynamic, and this may optimize its formation of the target proteins under many stimuli, containing pressure overload.

A recent study has demonstrated that nNOS enhances cGMP/PKG-dependent phosphorylation of cardiac troponin I and cardiac myosin binding protein C and contributes myocyte relaxation in hypertension via cGMP/PKG-dependent myofilament Ca2+ desensitization (30) (Figure 1). Myofilament proteins are the targets of nNOS that mediate relaxation in cardiac myocytes to decrease the myocardium in hypertensive heart. Exogenous NO donors ease myocardial relaxation through sGC and cGMP/PKG-dependent phosphorylation of cTnI and myofilament Ca2+ desensitization [75]. A recent report has shown that NO mimetics diminish myofilament Ca2+ sensitivity and contractility by causing the S-nitrosylation of many myofilament proteins containing actin, myosin, and troponin C (cTnC) [76]. These results suggest that phosphorylation and the myofilament proteins are the fundamental mechanisms that mediate the effects of nNOS in the heart. nNOS is considered as the isoform that is stated in the mitochondria to organize cardiac metabolism [76]. NO inhibits cytochrome c oxidase activity by competing with O2 and inhibits electron transfer of complex III or NADH-dehydrogenase function at the level of complex I and enhances mitochondrial formation of O2 -. Eventually, NO inhibits the mitochondrial respiration chain and diminish mitochondrial oxygen consumption [77-83]. In this respect, NO has been approved as a regulator of mitochondrial activity and metabolism. Even so, conditional overexpression of nNOS in the myocardium has related to enhanced nNOS in the mitochondria and a reduction in oxidative stress following myocardial infarction [51]. The modulation of oxidative stress by endogenous nNOS in diseased hearts can be a protective mechanism. Emerging evidence demonstrates that nNOS-derived NO plays leading roles in mitochondrial biogenesis [84,85], to maintain or enhance mitochondrial integrity and activity. For example, nNOS has been shown to be distributed to the nucleus through α-syntrophin via its PDZ domain in a variety of cells, containing myocytes [33,86]. Enhanced S-nitrosylation of nuclear proteins, containing cAMP response element-binding protein (CREB), in interacts with the promoter of the gene encoding peroxisome proliferator-activated receptor γ coactivator (PGC)-1α promoter, a central component of biogenesis and nuclear respiratory factor 1 [33]. NO has also included in cardiac energetics by impressing carbohydrate metabolism of mitochondria (Figure 2).

Clinical usage

Nitroglycerin has been used clinically in the treatment of CVD for more than 150 years. Enhanced acknowledgment of the mechanistic insights into NO signaling, the decomposition of NO, and the properties of NOSs modern technology allows different attitudes to enhance NO bioavailability in tissues for the desired responses as well. In principle, enhancement of NO and its signaling can be succeeded via three ways: enhance sources to contribute NO production, reduce NO

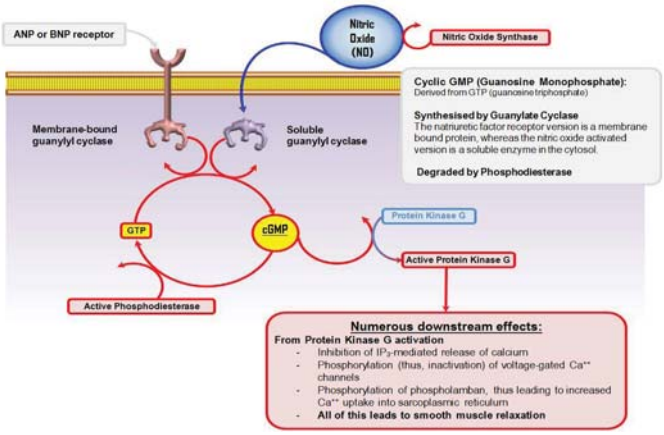

Figure 1: Demonstrated by Effect mechanisms of NO.

Figure 2: Demonstrated by Effective enzymes.

metabolism/degradation, and stimulate downstream signaling of NO. Delivering nitrate and nitrite to step up systematic or local NO via nitrate–nitrite–NO and the nitrate–nitrite–NO–fatty acid pathways are arguably the most active area under investigation experimentally and in the clinic [10]. So far, some putative precursors of NO have been described and are developing. Dietary consumption of NO precursors is an efficient way of nitrate delivery; programming of a suitable diet regime for vulnerable populations will be necessary to diminish the cardiovascular risks the economic burden on national healthcare systems as well. The correlation between the daily consumption of nitrate and cardiovascular events is notable. For instance, high vegetable units received in Japanese historically recognised have low rates of CVD is related to greater circulating nitrate and nitrite [87], contrasted to those in the western world, where average daily nitrate intake ranges from 40–100 mg and 30–180 mg, respectively, and the rates of CVD are high [88,89]. Moreover, the use of "healthy" fats, as in the Mediterranean diet, in the form of unsaturated fatty acids, is useful in preventing the development of CVD and decreases the risk factors [90]. Especially, nitrite reduction to NO happens in the presence of hypoxia and acidosis, during physical exercise, at the time when the cardiac muscle needs NO. In rotation, supplementation of NO substrates, e.g. arginine, L-citrulline, and BH4, and inhibition of arginase and

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asymmetric dimethylarginine are the strategies to enhance NO via promoting NOS activity [11]. Statins and nebivolol or carvedilol exert antiadrenergic responses through the stimulation of the beta3-adrenergic receptor and increasing NOS production of NO [91–94]. Waning the generation of ROS use blockers of angiotensin-converting enzyme (ACE), angiotensin I type 1 receptor (AT1R), or NADPH oxidases (NOXs) or decreasing ROS by use antioxidants and scavengers are the assumed mechanisms to diminish NO "sink" and thus maintain or increase NO level [11]. As such, it is wrong only to assume that NO level can be enhanced by use ACE and AT1R inhibitors. The development of NOX inhibitors and specific ROS manipulating drugs that do not affect NOS protein should follow, and the effect of NOX and ROS on nNOS protein expression in the myocardium should be considered. Stimulation of the downstream signaling pathway of NO is a recovered strategy to target the effector proteins. The oral sGC stimulators, and atrial, brain, and C-type natriuretic peptides are in using to enhance cellular Cgmp [11]. Inhibition of a negative regulator of cGMP, PDE5 is another therapeutic approach to stimulate cGMP/PKG signaling [95-97]. Stimulation of the PKG-dependent pathway has been demonstrated to exert potent protective effects in a broad range of cardiovascular disease models, including hypertension, PAH, heart failure, hemolytic anemia, and infarct-reperfusion injury [95-99]. But, the application of the drugs in a large cohort of patients with CVD demonstrate responses to the treatment. Some validated ways have been developed to enhance systemic and local NO levels and are promising in mediating the beneficial effects in CVD. But, to translate the research innovations into the application to a large population, more research is necessary, with particular attention to the effectiveness of the diet and strategies of increasing nNOS and improving NO-effector interactions in CVD settings. The NO and NOSs regulate myocardial contraction, relaxation, and pathological signaling are advanced, but the changing paradigm in the myocardium is not offered. NO from sources supplying the NO in the myocardium, and effectiveness of NO is confirmed by regulation mechanisms containing daily consumption of NO precursors, nitrate from skeletal muscles, NO production through the entire salivary NO pathway and from NOSs as well as the abundance of target proteins. In general, NO regulates downstream effector proteins through three mechanisms (sGC/cGMP/PKG-dependent phosphorylation, S-nitrosylation, and trans-nitrosylation) and the numbers and types of effectors regulated by NO are diverse. As such, modification of these effectors by NO subsequently triggers an array of signaling cascades that lead to different physiological and pathological consequences. By and large, NO and its downstream signaling pathway exert high cardiovascular protection; but, research of NO and NOS that are feasible for CVD and therapeutic efficiency using an NO-dependent regime are still far from satisfactory [11].

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