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# Implications of Nitric Oxide in Diseased and Healthy Conditions: Dependent Factors and Health Benefits Optimization Options

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## Abstract

Nitric oxide (NO), a free gaseous radical with a short life of few seconds (6-30s), is produced through the oxidative reaction of L-arginine, catalyzed by nitric oxide synthases (NOS). NO regulates and mediates various pathophysiological statesincluding in the nervous, immune and cardiovascular systems, through the activation of soluble guanylate cyclase among other mechanisms. Reported physiological functions of NO include vascular smooth muscle relaxation (which results in vasodilation of arteries and increase in blood flow), macrophage toxicity against microbes and tumor cells and neurotransmission (neuronal activities). The pathological effects of NO include tissue damage associated with acute and chronic inflammations and toxic effect under oxidative conditions, which may be as a result of its possible conversion into highly reactive peroxynitrite in several nervous system disorders and endothelial dysfunctions when over produced.Thus, the implications of NO in diseased and healthy conditions, the dependent factors and the health benefits optimization optionswere reviewed by keying in appropriate search words in regular search engines, including Google. As deciphered from the review, NO was variably implicated in varied diseased and healthy conditions. The variations seem to depend on the NO concentration, site of production and the particular nitric oxide synthase isoform involved in the synthesis of NO. Thus, optimization of the potential health benefits of NO could be achieved through the optimization of NO concentration synthesized at the appropriate site by the appropriate isoform of NOS. Empirical studies in these directions as suggested are warranted and so recommended.

## Keywords

Nitric oxide synthase; Peroxynitrite; Cytotoxic; Free radical; Antioxidant

## Introduction

Nitric oxide, NO, has a single electron and is readily oxidized to nitrite ($NO_2$) and nitrate ($NO_3$), hence a free gaseous radical with a short half-life of few seconds [1]. Nitric oxide is readily distributed in the cell where it could exert a wide range of interactions including with metals incorporated in enzyme structure, heme, superoxide and oxygen. Nitric oxide (NO) is one of the products of the nitric oxide synthases (NOS) catalyzed monoxygenation/ oxidative reaction of L-arginine [2]. In the first step of the reaction cycle, initiated by the displacement of caveolin-I from the NOS when calcium ion complexes with calmodulin to form calcium-calmodulin complex to trigger on the constitutive forms of nitric oxide

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synthase, L-arginine is oxidized to the stable intermediates N-hydroxyl-L-arginine which is then oxidized to nitric oxide (NO) and citrulline [2,3].

As a free radical, NO is cytotoxic notably following its excessive production [4,5]. However, at optimal concentration, nitric oxide offers a whole lot of physiological benefits. For instance, NO acts as antioxidants to combat oxidative stress that is fundamental to disease and health conditions [6]. Reduction of the bioactive concentration of nitric oxide following increased concentration of reactive oxygen species (ROS) and concomitant formation of toxic peroxynitrite[7,8] had implicated the loss of nitric oxide production and subsequent bioavailability with various disease conditions including diabetes, hypertension and hypercholesterolemia [9]. Thus, the free radical status yet antioxidant property of NO warranted this review aimed at assessing the implications of NO in diseased and healthy conditions, the dependent factors that determine the cytotoxic, pathological and health benefit effects of NO *vis a vis* the NO health benefits optimization options. The objectives to achieving the review aim were by keying in appropriate search words in regular search engines, including Google.

## Understanding the nitric oxide synthase (NOS) isoforms, sites and classification

Nitric oxide synthases (the enzyme involved in NO release) has many isoforms. Understanding the nitric oxide synthase isoforms and sites is fundamental to understanding the involvement of NOS in NO synthesis and the peculiar synthesized concentration, opposing properties and functions of nitric oxide. The three major nitric oxide synthase isoforms involved in the synthesis of nitric oxide in mammals are neuronal (NOSI or nNOS), inducible or macrophagal (NOSII or iNOS) and endothelial (NOSIII or eNOS) [3,10,11].

The major site of macrophagal or inducible NOS (iNOS) is in the activated neutrophils and macrophages, astrocytes and hepatocytes. It is not constitutively expressed and is involved in the early immune responses. Inducible NOS is induced at the transcriptional levels of cytokinesand exotoxins to generate extraordinary high concentrations of nitric oxide that could kill bacteria. Hence, iNOSis usually expressed under certain conditions such as inflammation due to injury or infectious process [12]. As such, iNOS synthesizes excessive NO to act as potent cytotoxin by destroying pathogens engulfed by neutrophils and macrophages thereby controlling intracellular pathogens such as parasites, schistosoma, toxoplasma, microbial fungi and tumour cells [13,14]. In addition, at such a high concentration, iNOSby producing equally high concentration of NO has neurotoxic effects. However, at low concentration, iNOS produces low concentration of NO hence has neuroprotective effects and mediates beneficial physiological signaling. Thus, the cytotoxic reactions of nitric oxide may result mainly from that catalyzed by the inducible nitric oxide synthase isoform located in the macrophages, astrocytes, neutrophils and hepatocytes.

The primary site of neuronal NOS (nNOS) is in the skeletal muscles and in the neurons of both the central and peripheral nervous systems. It is constitutively expressed and produces nitric oxide that serves as a neurotransmitter in the central and peripheral nervous systems. Neuronal NOS also serve as mediator of contractile force in the skeletal muscle, innervations of developing muscle and glucose uptake in the skeletal muscle. It is activated by calcium influx through voltage dependent calcium channels.

As the name suggests, the primary site of endothelial NOS (eNOS) is in the vascular endothelial cellslining the blood vessels and cardiac myocytes hence localized in the membrane. As the nNOS, eNOSis constitutively expressedandactivated by influx of calcium through the voltage dependent calcium channels.The nitric oxide produced by eNOS acts as a vascular dilator of smooth muscle and knocking out the gene for (hence inhibiting the expression of) this isoform results in an increase in blood pressure.

Other isoforms of NOS, aside the aforementioned, include the mitochondrial NOS (mNOS), osteoarthritic NOS (oNOS) and guinea pig inducible NOS (gpiNOS) [15].Thus, generally, the isoforms of nitric oxide synthase (NOS) are classified as endothelial nitric oxide synthase, neuronal nitric oxide synthase, macrophagal or inducible nitric oxide synthase as described above. However, based on the mechanisms of action, NOS enzymes are broadly classified as constitutive nitric oxide synthase and inducible nitric oxide synthase. Constitutive forms are the nNOS and eNOS while the inducible form is the macrophagal or inducible nitric oxide synthase.

The constitutive isoforms of NOS are dependent on Ca2+/ calmodulin concentration and are extremely important in the regulation of physiological processes. The non-constitutive or inducible formsare synthesized in cells only after induction by such inflammatory mediators

as tumor necrosis factor (TNF-α), lipopolysaccharides (LPS), interleukins (IL-I, IL-II) bacterial endotoxins. The non-constitutive or inducible isoforms of NOS do not depend on Ca2+/calmodulin concentration and are being considered as pathological isoforms of NOS[1].

All isoforms catalyze the same reactions, but every one of them has its own unique structure and localization. These features determine differences of activation pathways as well as specificity of inhibitors. Each isoform synthesizes nitric oxide under specific condition and may all be present in a particular cell. The characteristic features of nitric oxide and functional differences among the nitric oxide synthase isoforms determine its different role in regulation of many physiological and pathological processes. Thus, the production site of NOS and the particular isoform of NOS are fundamental to functions of the NO produced – whether cytotoxic, pathological or beneficial to health. However, as NOS isoforms are named or classified based on location or site, type and site of NOS isoforms are almost used interchangeably.Calcium-calmodulin complex formation and NO synthesis

The activation of eNOS and nNOS following the influx of calcium through the voltage dependent calcium channels involves the excitatory action of glutamate resulting to eventual calcium-calmodulin complex formation that triggers the NOS [2, 16]. This is a very important event in NO synthesis and actions. For instance, at low cytoplasmic calcium concentration, caveolin-I binds to endothelial nitric oxide synthase thereby inhibiting it or restricting eNOS to its inactive state. However, with calcium influx hence increased cytoplasmic calcium concentration, calmodulin complexes with calcium to competitively displace the calveolin-I from eNOS thereby resulting in activation of nitric oxide synthase [16].

The eventual synthesis of nitric oxide (NO) involves two monooxygenation reactions between molecular oxygen and L-arginine. In the first step, arginine is oxidized to the stable intermediates N-hydroxyl-L-arginine that is then oxidized to nitric oxide (NO) and citrulline [2,3]. L-arginine could be regenerated from citrulline for instance *via* the reactions of the urea. Thus, L-arginine and citrulline bioavailability is important in the steady biosynthesis hence bioavailability of NO.

## Mechanism of action of nitric oxide

Generally, nitric oxide acts as a free radical to mediate cytotoxic effects and and as an antioxidant to mediate beneficial physiological functions. Moreover, many of the physiological functions of nitric oxide are mediated through:

**(a)** Activation of soluble guanylate cyclase on binding to the $Fe^{2+}$ of the heme part of the guanylate cyclase subsequently converting guanosine triphosphate (GTP) to cyclic guanosine monophosphate (cGMP), a secondary messenger, that activates the cGMP-dependent protein kinase G (PKG). These series of biochemical events are fundamental to NO-mediated smooth muscle relaxation and inhibition of platelet aggregation [17]as well as further phosphorylation of many proteins[18].

**(b)** Activation of potassium channels in smooth muscles, neurons and endothelial cells, which are independent of cGMP mediation subsequently hyperpolarizing the membranes with a concomitant decrease in calcium ion levels. This could subsequently inhibit nitric oxide synthesis due to reduced chances of calcium-calmodulin complex formation and eventually inhibiting NO synthesis and NO-mediated activities including smooth muscle relaxation.

## Implication of nitric oxide in the mediation of diseased/pathological and Healthy/physiological conditions

A diseased or pathological state is a state of abnormal physiological functions, including of organs, part, structure or system of the body because of adverse internal or external factors. On the contrary, ahealthy or physiological state is a state of normal physiological functions of the whole body parts and organs due to prevailing normal internal and external factors.

### (a) High and low NO concentration

At high concentration (resulting from excessive synthesis) NO could elicit either pathological [4,5] hence undesirable (pro-inflammatory action) including tissue damage associated with acute and chronic inflammation and toxic effects under oxidative conditions or physiological and beneficial/desirable (antiviral, antibacterial, antiparasitic) effects. In particular, pathological effects of NO may be because of its possible conversion into highly reactive peroxynitrite in several nervous system disorder and endothelial dysfunction when overproduced [19].

Essentially, at low concentrations, nitric oxide mediates various physiological functions in humanthrough the activation of soluble guanylate cyclase. These

include vascular smooth muscle relaxation that results in vasodilation of arteries and increase in blood flow[20], neurotransmission involved in neuronal activities and other functions such as learning and memory processes [21] and the mediation of macrophage toxicity against microbes and tumor cells [22,23]. Thus, depending on the concentration, NO could be either beneficial or otherwise. It is therefore important to note the prevailing rate of synthesis and attendant concentration NO in different systems to minimize undesirable effects while maximizing or optimizing desirable effects of NO [24].

**(b) Neuroprotection and neurotoxicity**

Nitric oxide as a gas cannot be stored in synaptic vesicles hence when synthesized in the central nervous system as catalyzed by the neuronal nitric oxide synthase (nNOS), it diffuses readily into the neighboring neurons to, depending on prevailing concentration, exerts neuro-modulatory, neuroprotective or neurotoxic effects[25-27]. In particular, the pathological or toxic implication of excess NO synthesized as catalyzed by nNOS include neuronal damage and neurodegradative diseases including Parkinsondisease,Alzheimer disease, dementia and Huntington disease. Hence, NO synthesis in the central nervous system should be down regulated to avoid overproduction.

**(c) Gastrointestinal motility and sphincter contractility**

Nitric oxide synthesized in the myenteric plexus of stomach, intestines lower esophageal, ileocolic, and intestinal anal sphincter enhances the stimulation of mucus secretion into the gut and dilation of the stomach at physiological conditions. Overall, the inhibition of endogenous production of NO improves gastrointestinal motility and modulates the contractility of sphincter while its increased production reduces the contractility of sphincters, which could be optimized in the therapeutic management of for instance gastro esophageal reflux disease [28,29].This could be attributed to nitric oxide-related defensive role on the mucosal immunity including the regulation of the mucosal blood perfusion, stimulation of gastric mucus secretion, reduction of adherence of leukocytes and inhibition of mast cells activation [30].

**(d) Endothelial dysfunction and vasodilation**

Impaired NO bioavailability due decreased production or increased breakdown of nitric oxide results in endothelial dysfunction and subsequent development of vascular diseases[16,31, 32]. Endothelial dysfunction underlies many pathological conditions including hypertension; diabetes mellitushypercholesterolemia [30] hence could be a good control cum optimization point for NO synthesis and health benefits.

**(e) Immune response, inflammation modulation and septic shock**

Nitric oxide synthesized by inducible nitric oxide synthase (iNOS) is a potent cytotoxin that destroys pathogens engulfed by macrophages and neutrophils. Thus, NO inhibits the growth and adverse activities of intracellular pathogens including parasites (schistosoma, leishmania, toxoplasma, microbial and mycobacteria), fungi and even tumor cells. Nitric oxide at cytotoxic concentration could react with oxygen to form toxic intermediates including peroxynitrate and superoxide known to cause DNA damage, strand cleavage, deamination and other modifications that could affect vital metabolic enzymes of, thereby causing cytotoxic and cytostatic effects against, these pathogens [33].

Nitric oxide modulates or mediates inflammation response to destroy or inactivate invading organism, remove irritants and set the stage for tissue repair [34]. However, at such cytotoxic concentration, nitric oxide was implicated in septic/cytotoxin-induced circulatory shock, ischemic reperfusion, atherosclerosis and hypertension [35]. For instance, at high concentration, NO might interact with other NO oxide molecules to form toxic peroxinitrite at the expense vasculardilation leading to vascular-constriction hence hypertension.

**(f) Hypertension**

An increased arterial pressure [36] characterizes hypertension, a major risk factor for stroke, heart failure, myocardial infarction and kidney failure. Generally, nitric oxide through its vascular dilatation action increases the volume of the arterial wall and based on the inverse relation of volume and pressure reduces the blood pressure. Nitric oxide bioavailability was impaired in hypertensive subjects and experimental animal models [37-39]. Thus, nitric oxide could play a major role in the regulation of blood pressure.

**(g) Atherosclerosis**

Atherosclerosis is a chronic inflammatory process in the arteries, whichis characterized by the impaired endothelium-dependent regulation of the vascular tone by

nitric oxide and thought to result from the oxidation of low-density lipoproteins in the arterial wall by reactive oxygen species [40,41].Atherosclerosis could predispose animals to further health dangers including hypertension, chronic kidney disease, stroke and angina, hypercholesterolemia and diabetes mellitus.When the vascular tissue level of tetrahydrobiopterin ($BH_4$) (a cofactor for nitric oxide synthase) is lacking there is a defect in eNOS, superoxide is produced rather than the nitric oxide which is made up of anti-atherogenic molecule [42-44].

**(h) Erectile dysfunction**

Erectile dysfunction, the inability to obtain or maintain the erection maximum for satisfactory sexual performance, is more prevalent in patients with diabetes mellitus, hypertension, hypercholesterolemia, atherosclerosis and renal failure [45, 46], which are known to be associated with endothelial dysfunction. Nitric oxide mediated smooth muscle relaxation and enhanced blood flow hence could play a crucial role in the physiology and pathophysiology of penile erection for instance by the activation of guanylate cyclase [47-49].

Generally, low levels of testosterone, which results to erectile dysfunction development,could occur particularly by increasing smooth muscle apoptosis, reducing erectile tissue relaxation and reducing nitric oxide bioavailability [50]. The phosphodiesterase-type 5 (PDE-5) inhibitors such as sildenafil, tadalafil and verdenafil used in the treatment of erectile dysfunctionact by inhibiting the PDE-5 enzyme from metabolizing cGMP thereby increasing the concentration of cGMP therebyenhancing nitric oxide synthesis and concentration as well as stronger and maximum erection through enhanced blood flow to the penile organ [50].

**(i) Diabetes and lowered insulin concentration**

In diabetic patients, endothelial dysfunctionwas accompanied by a decrease in the production of nitric oxide hence a fall in plasma NO concentration, impaired nitric oxide derived endothelium dependent relaxation and a marked fall in insulin with concomitant elevation in glucose, lactate and ketone bodies [2,51-53]. Further implication of NO in diabetes and lowered insulin concentration was the noted reliance of individuals with type 2 diabetes on NO for glucose uptake during exercise following impaired insulin-stimulated skeletal muscle glucose uptake [54] and the L-arginine-improved insulin sensitivity in diabetic patients [55].These were substantiated by the stimulatory effect of NO donors including sodium nitroprusside, on skeletal muscle glucose uptake [54] and the involvement of AMP-activated protein kinase, protein kinase C, nitric oxide and calcium in muscle contraction-mediated glucose uptake[56-58].

Since NO bioavailability, which is a major determinant of vascular homeostasis, is reduced in diabetes, steps to enhancing NO synthesis and availability could optimize health benefits in cases of diabetes and perhaps in other diseased conditions. It is therefore important to note the specific action of nitric oxide in different systems to minimize undesirable effects and maximize or optimize desirable effects for pharmacological applications [24]. Hence, it is pertinent to identify the possible control points for nitric oxide synthesis and related health benefits optimization.

**Possible control points for nitric oxide synthesis and health benefits optimization of nitric oxide**

Identification of the possible control points for nitric oxide synthesis and health benefits optimization entails a holistic exploration of the NO oxide synthetic mechanisms. And, as could be deciphered from the foregoing, the control points for the synthesis and activities of NO, hence the health benefits optimization of NO would be at the levels of NOS isoforms (selecting the optimal NOS isoform), the site of the NOS isoforms involved in NO synthesis, the calcium and potassium pumps, and even augmenting NOS cofactor, $BH_4$ levels. Other control or regulation points for the synthesis and activities of NO as well as health benefit optimization include:

**(a)** Inhibition by L-arginine derivatives, including N-monomethyl-l-arginine (L-NMMA) and N-nitro-L-arginine methyl ester (L-NAME) which non-selectively competes with L-arginine to inhibit the activity of the nitric oxide synthases in synthesizing NO from the lone precursor, L-arginine [9] as well as L-canavanine and N-omega-cyclosporin-L-arginine which selectively inhibits iNOS and eNOS from synthesizing NO [9].

**(b)**Competitive inhibition of calmodulin receptors by calmodulin antagonists including calmidazolium, chlorpromazine and trifluoperazine specifically that inhibit all NOS dependent $Ca^{2+}$/ calmodulin (nNOS and eNOS) to prevent NO synthesis and actions.

**(c)** The inhibition by nitric oxide itself (negative feedback

mechanism) through NO/NOS heme group reactions.

**(d)**Through the influence of the NOS cofactor, tetrahydrobiopterin ($BH_4$) that is crucial for proper functioning of all NOS isoforms.This is particularly important control and optimization point since insufficient $BH_4$levels resulted to its oxidization todihydrobiopterin ($BH_2$) form consequently resulting to the uncoupling of notably the eNOS from the oxidation of L-arginine hence the production of superoxide ($O_2^-$) rather than NO [59]. This superoxide could readily react with NO to form toxic peroxynitrite[7, 8], further reducing NO bioavailability.

**(e)**Through the control and optimization of arginase bioavailability. This is because;L-arginine aside being the substrate for NOS is also the substrate for the arginase enzyme, which converts it (L-arginine) to ornithine thereby limiting L-arginine availability for NO synthesis and bioavailability [58].

**(f)** Through the control and optimization of the oxidant and pro-oxidant balance to prevent onset of oxidative stress. This is important, as oxidative stress is fundamental to diseased and healthy conditions with increased and reduced oxidative stress respectively indicating diseased and healthy conditions[6]. Further to this, the reduction of the bioactive concentration of nitric oxide following increased concentration of reactive oxygen species (ROS), hence increased oxidative stress [7,8] had implicated decreased nitric oxide production and subsequent bioavailability with various disease conditions including diabetes, hypertension and hypercholesterolemia [9].

## Conclusion

As deciphered from the review, NO was variably implicated in varied diseased and healthy conditions. The variations seem to depend on the NO concentration, site of production and the particular nitric oxide synthase isoform involved in the synthesis of NO. Thus, optimization of the potential health benefits of NO could be achieved through the optimization of NO concentration synthesized at the appropriate site by the appropriate isoform of NOS. Empirical studies in these directions as suggested are warranted and so recommended.

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