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Review Article

REVIEW ON PHYSIOLOGICAL AND PATHOLOGICAL ROLE OF NITRIC OXIDE

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ABSTRACT

Nitric oxide is a unique biological messenger molecule. It is a small highly diffusible gas and a ubiquitous bioactive molecule. Its chemical properties make NO a versatile signal molecule that functions through interactions with cellular targets via either redox or additive chemistry. It mediates, in part, the immune functions of macrophages, it is produced by endothelial cells to mediate blood vessel relaxation; and it also serves as a neurotransmitter in the central and peripheral nervous system. Endothelial nitric oxide synthase and neuronal nitric oxide synthase are thought to be primarily constitutive, with activation induced by calcium entry into cells in the absence of protein synthesis, whereas the macrophage nitric oxide synthase is inducible with large increases in new nitric oxide synthase protein synthesis after immune stimulation. In plants, NO plays a role in a broad spectrum of pathophysiological and developmental processes. The molecular targets of nitric oxide are expanding, as are its physiological and pathophysiological roles in the nervous system. Nitric oxide may regulate neurotransmitter release, and it may play a key role in nervous system morphogenesis and synaptic plasticity and regulate gene expression. Under conditions of excessive formation, nitric oxide is emerging as an important neurotoxin in a variety of disorders of the nervous system.

KEYWORDS: *Nitric oxide synthase, Chemical mediator, Endothelium derived relaxing factor.*

INTRODUCTION

Nitric oxide, or nitrogen oxide so known as nitrogen monoxide, is a molecule with chemical formula NO. It is a free radical and is an important intermediate in the chemical industry [1, 2]. In mammals including humans, NO is an important cellular signaling molecule involved in many physiological and pathological processes. It is a powerful vasodilator with a short half-life of a few seconds in the blood. Long-known pharmaceuticals such as nitroglycerine and amyl nitrite were discovered, more than a century after their first use in medicine, to be active through the mechanism of being precursors to nitric oxide. Low levels of nitric oxide production are important in protecting organs such as the liver from ischemic damage. Nitric oxide should not be confused with nitrous oxide (N_2O), an anaesthetic and greenhouse gas, or with nitrogen dioxide (NO_2), a brown toxic gas and a major air pollutant. However, nitric oxide is rapidly oxidised in air to nitrogen dioxide.

Despite being a simple molecule, NO is an important biological regulator and is a fundamental component in the fields of neuroscience, physiology, and immunology, with discovery of its key roles leading to Nobel Prize-winning research in these areas. It was proclaimed "Molecule of the Year" in 1992. Nitric oxide is a gas. It is highly reactive; that is, it participates in many chemical reactions. (It is one of the nitrogen oxides ("NO_x") in automobile exhaust and plays a major role in the formation of **photochemical smog.** Nitric oxide (NO) readily diffuses across cell membranes and regulates a wide range of physiologic and pathophysiologic processes, including, cardiovascular, inflammation, immune and neuronal functions [3].

Discovery of Endogenous Nitric Oxide:

Early observations of the biologic role of endogenously generated NO were made in rodent macrophages and neutrophils: In vitro exposure of these cells to endotoxin lipopolysaccharide released significant amounts of nitrite and nitrate into the cell culture medium. Furthermore, injection of endotoxin in vivo elevated urinary nitrite and nitrate, the two oxidation products of nitric oxide. This nitric oxide was found to

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originate from oxidation of the guanidino group of L-arginine [4]. The second observation was made by Furchgott and Zawadzki in 1980 using isolated vascular smooth muscle preparations [5]. They discovered that following stimulation with acetylcholine or carbachol, the endothelium released a short-lived vasodilator, which unlike endothelium-derived prostacyclin was not blocked by cyclooxygenase inhibitors. They named this vasodilator endothelium-derived relaxing factor (EDRF) since it promoted relaxation of precontracted smooth muscle preparations. Other workers confirmed and extended these findings. In 1987, by comparing the pharmacologic and biochemical properties of the suspect molecule, three independent groups reported that EDRF and nitric oxide is the same molecule. It was later reported that other vasodilator molecules may be a part of EDRF, but it appears clear that nitric oxide provides the major part of its activity. Subsequent studies revealed that nitric oxide was generated by many cells and was, like the eicosanoids, found in almost all tissues [6].

Characteristics of NO:

Summary of NO's Properties

1. Gas that freely diffuses through membranes
2. Short-lived with a half-life measured in seconds
3. Highly reactive free radical
4. Toxic at high concentrations

NO is a short-lived gas not to be confused with the relatively stable anesthetic gas nitrous oxide (laughing gas). NO is actually a free radical and is therefore a highly reactive compound. Some of its toxic effects are likely due to NO reacting with superoxide to produce the destructive radical peroxy nitrate. NO is considered an unconventional neurotransmitter because it is not released by exocytosis and its action does not occur through conventional receptor molecules. A presynaptic neurotransmitter is released that produces changes in the postsynaptic neuron. Several compounds (like neuropeptides and NO) produced in postsynaptic neurons diffuse into the local environment and affect the surrounding cells. Since NO is a freely diffusible gas it has the potential to travel quickly in any direction from its point of production. For example, if produced in a postsynaptic cell because of glutamate receptor stimulation, NO could be released into the local environment and send a signal back to the presynaptic neuron. This type of activity is referred to as retrograde signaling since the signal travels in a retrograde direction from the postsynaptic to the presynaptic neuron.

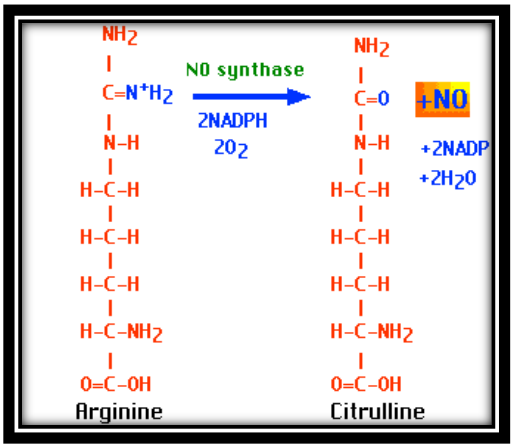
Features:

NO is synthesized within cells by an enzyme NO synthase (NOS).The human (and mouse) genome contains 3 different genes encoding NO synthases.

nNOS (or NOS-1): found in neurons (hence the "n").

eNOS (or NOS-3): found in the endothelial (hence the "e") cells that line the lumen of blood vessels.

iNOS (or NOS-2): found in macrophages. (the "i" stands for "inducible"). Whereas the levels of nNOS and eNOS are relatively steady, expression of iNOS genes awaits an appropriate stimulus (e.g., invasion by a pathogen). All types of NOS produce NO from arginine with the aid of molecular oxygen and NADPH. There are so many other molecules, with which it can interact, that it is quickly consumed close to where it is synthesized. Thus NO acts in a paracrine or even autocrine fashion affecting only cells near its point of synthesis.



Nitric Oxide Synthesis:

It is synthesized by a family of enzymes that are collectively called nitricoxide synthase. This enzyme is found in a subpopulation of neurons (1-2% of neurons in cortex) and is found in most all endothelial cells [16]. Nitric oxide synthases (NOSs) synthesize the metastable free radical nitric oxide (NO). There are three isoforms of the NOS enzyme: endothelial (eNOS), neuronal (nNOS), and inducible (iNOS) - each with separate functions. The neuronal enzyme (NOS-1) and the endothelial isoform (NOS-3) are calcium-dependent and produce low levels of this gas as a cell signaling molecule. The inducible isoform (NOS-2) is calcium independent and produces large amounts of gas which can be cytotoxic. These isoforms are heme-containing flavoproteins employing L-arginine as a substrate and requiring NADPH (nicotinamide adenine dinucleotide phosphate, FAD (flavin adenine mononucleotide), FMN (flavin mononucleotide), and tetrahydrobiopterin as cofactors. These cofactors are essential for the transfer of electrons that produces the unstable and short-lived product NO. NOS oxidizes the guanidine group of L-arginine in a process that consumes five electrons and results in the formation of NO with stoichiometric formation of L-citrulline. The process involves the oxidation of NADPH and the reduction of molecular oxygen. The transformation occurs at a catalytic site adjacent to a specific binding site of L-arginine [10].

Phosphorylation also has differential regulatory effects on the activity of NOS. For example, phosphorylation significantly reduces the activity of NOS-1, whereas phosphorylation of NOS-3 by a serine-threonine protein kinase activates the enzyme. Furthermore, NOS-2 expression is tightly controlled by several transcription factors.

Figure-1

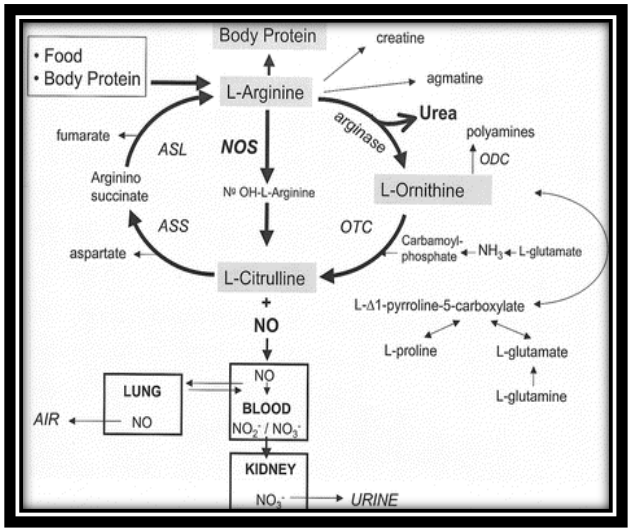


Table No. 1: Properties of the Three Isoforms of Nitric Oxide Synthase (NOS)

	eNOS	nNOS	iNOS
Originally cloned from	Endothelial cells	Neuronal cells	macrophages
Tissue expression	Cardiac myocytes Platelets neurones	Skeletal muscle, neutrophils,VSMC*	Cardiac myocytes, Glial cells, VSMC*, endothelium, neurons
Gene encoding and its position	NOS3 7q35-36	NOSI 12q24.2-31	NOS2 17q11.2-12
Major regulatory mechanism	Ca^{+2} dependent (Ca-calmodulin) Ca^{+2} independent (phosphorylation, palmitoylation)	Ca^{+2} dependent (Ca-dystrophin)	Ca^{+2} independent; transcriptional regulation e.g.by NFB
Subcellular localization	Golgi apparatus Plasmalemmal Caveolac	Cytosol Endoplasmic reticulum Sarcollema Postsynaptic densities Caveolae(caveolin 3)	phagosomes

Non-Enzymatic Sources of NO:

Currently, exogenous NO sources constitute a powerful way to supplement NO when the body cannot generate enough for normal biological functions. So, recent developments of novel NO donors, NO releasing devices as well as innovative improvements to current NO donors have been investigated [7]. It should be noted that certain endogenous compounds can act as NO-donors or elicit NO-like reactions *in vivo*. Prominent examples are S-nitrosothiols, certain organic nitrates, nitrosylated metal complexes, dinitrosyl-iron complexes (DNIC), oreven nitrite anions under hypoxic conditions [8, 9].

Activation of NOS by the influx of extracellular calcium and binding of calmodulin, as in the case of the constitutive enzyme, or following the activation of the inducible NOS (NOS-2) by cytokines, results in the metabolism of L-arginine to L-citrulline and nitric oxide. The conversion of L-arginine to nitric oxide and L-citrulline is inhibited by several arginine competitors such as *N*G-monomethyl-L-arginine. Some nitric oxide donors, eg, oxygenated nitroprusside, spontaneously generate such as nitroglycerin, require the presence of a thiol compound such as cysteine. Once generated, nitric oxide interacts with the heme moiety of soluble guanylyl cyclase in the cytoplasm of cells [11]. This results in allosteric transformation and activation of the enzyme and leads to the formation of 3',5'-cyclic-guanosine monophosphate (cGMP) from GTP. Activation of the soluble guanylyl cyclase by nitric oxide can be inhibited by methylene blue. The affinity of nitric oxide for iron is also responsible for its inhibitory effect on several enzymes by interacting with the iron-sulfur centers of these enzymes. Inhibition of enzymes such as cytochrome P450 by nitric oxide is a major problem in inflammatory liver disease and can be reversed by NO synthase inhibitors. Carbon monoxide, another gaseous compound produced endogenously from the catabolism of heme, shares many of the properties of nitric oxide such as activation of soluble guanylyl cyclase. However, unlike nitric oxide, which has an extra electron, carbon monoxide is astable molecule in the presence of oxygen. The affinity of nitric oxide for hemoglobin is severalorders of magnitude greater than that of carbon monoxide. Nitric oxide undergoes both oxidative and reductive reactions, resulting in the formation of a variety of oxides of nitrogen.

Inactivation:

Nitric oxide is inactivated by heme and by the free radical, superoxide. Thus, scavengers of superoxide anion such as superoxide dismutase may protect nitric oxide, enhancing its potency and prolonging its duration of action. Conversely, interaction of nitric oxide with superoxide may generate the potent tissue-damaging moiety, peroxynitrite (ONOO-), which

has a high affinity for sulfhydryl groups and thus inactivates several key sulfhydryl-bearing enzymes. This effect of peroxynitrite is regulated by the cellular content of glutathione. Since glutathione is the major intracellular soluble sulfhydryl-containing compound, factors that regulate the biosynthesis and decomposition of glutathione may have important consequences. Glutathione also interacts with nitric oxide under physiologic conditions to generate nitrosoglutathione, a more stable form of nitric oxide. Nitrosoglutathione may serve as an endogenous long-lived adduct or carrier of nitric oxide. Vascular glutathione is decreased in diabetes mellitus and atherosclerosis, and this may account for the increased incidence of cardiovascular complications in these conditions. Ischemia followed by reperfusion is another situation in which endothelial function is compromised owing to increased production of free radicals, resulting in reduced nitric oxide formation.

Inhibitors of Nitric Oxide:

In theory, several methods are available for reducing nitric oxide levels in tissues and thus inhibiting its actions. Drugs may inhibit the uptake of L-arginine into cells, thus depriving the NOS isoforms of substrate. Other methods include deprivation of the cofactors and calmodulin antagonists; inhibitors of NOS synthesis; inhibitors of binding of arginine to NOS, and scavengers of nitric oxide. The most important thus far have been inhibitors of NOS. Unfortunately, the selectivity of these inhibitors for the individual isoforms is incomplete. Most of these inhibitors are substrate analogs.

Mechanism of Action:

There are several mechanisms by which NO have been demonstrated to affect the biology of living cells. These include oxidation of iron-containing proteins such as ribonucleotide reductase and aconitase, activation of the soluble guanylate cyclase, ADP ribosylation of proteins, protein sulfhydryl group nitrosylation, and iron regulatory factor activation [12]. NO has been demonstrated to activate NF-κB in peripheral blood mononuclear cells, an important transcription factor in iNOS gene expression in response to inflammation [13]. It was found that NO acts through the stimulation of the soluble guanylate cyclase, which is a heterodimeric enzyme with subsequent formation of cyclic-GMP. Cyclic-GMP activates protein kinase G, which causes reuptake of Ca^{2+} and the opening of calcium-activated potassium channels. The fall in concentration of Ca^{2+} ensures that the myosin light-chain kinase (MLCK) can no longer phosphorylate the myosin molecule, thereby stopping the cross bridge cycle and leading to relaxation of the smooth muscle cell [14].

Figure-2

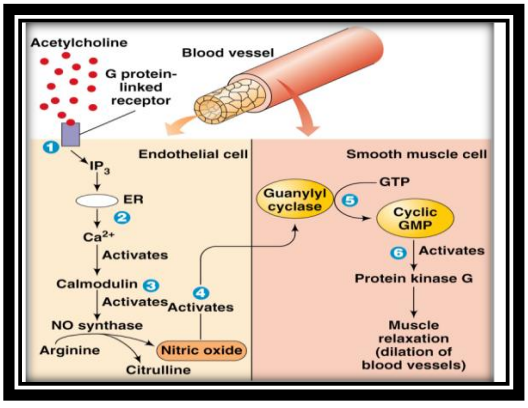


Table No. 2: Pharmacology

Pharmacology	
Bioavailability	Good
Routes of administration	Inhalation
Metabolism	via pulmonary capillary bed
Elimination half-life	2–6 seconds

This vasodilation does not decrease the volume of blood the heart pumps, but rather it decreases the force the heart muscle must exert to pump the same volume of blood. Nitroglycerin pills, taken sublingually (under the tongue), are used to prevent or treat acute chest pain. The nitroglycerin reacts with a sulfhydryl group (–SH) to produce nitric oxide, which eases the pain by causing vasodilation. Recent evidence suggests that nitrates may be beneficial for treatment of angina due to reduced myocardial oxygen consumption both by decreasing preload and after load and by some direct vasodilation of coronary vessels.

Pharmacokinetics:

Nitric oxide is absorbed systemically after inhalation. Most of it moves across the pulmonary capillary bed where it combines with hemoglobin that is 60% to 100% oxygen-saturated. Nitrate has been identified as the predominant nitric oxide metabolite excreted in the urine, accounting for >70% of the nitric oxide dose inhaled. Nitrate is cleared from the plasma by the kidney at rates approaching the rate of glomerular filtration.

Biological Functions of Nitric Oxide:

NO is one of the few gaseous signaling molecules known and is additionally exceptional due to the fact that it is a radical gas. It is a key vertebrate biological messenger, playing a role in a variety of biological processes. It is a known bioproduct in almost all types of organisms, ranging from bacteria to plants, fungi, and animal cells. Nitric oxide, known as the 'endothelium-derived relaxing factor', or 'EDRF', is biosynthesized endogenously from L-arginine, oxygen, and NADPH by various nitric oxide synthase (NOS) enzymes. Reduction of inorganic nitrate may also serve to make nitric oxide. The endothelium (inner lining) of blood vessels uses nitric oxide to signal the surrounding smooth muscle to relax, thus resulting in vasodilation and increasing blood flow. Nitric oxide is highly reactive (having a lifetime of a few seconds), yet diffuses freely across membranes. These attributes make nitric oxide ideal for a transient paracrine (between adjacent cells) and autocrine (within a single cell) signaling molecule [15].

The production of nitric oxide is elevated in populations living at high altitudes, which helps these people avoid hypoxia by aiding in pulmonary vasculature vasodilation. Effects include vasodilatation, neurotransmission , modulation of the hair cycle, production of reactive nitrogen intermediates and penile erections (through its ability to vasodilate). Nitroglycerin and amyl nitrite serve as vasodilators because they are converted to nitric oxide in the body. The vasodilating antihypertensive drug minoxidil contains an NO moiety and may act as an NO agonist. Likewise, Sildenafil citrate, popularly known by the trade name *Viagra*, stimulates erections primarily by enhancing signaling through the nitric oxide pathway in the penis. Nitric oxide (NO) contributes to vessel homeostasis by inhibiting vascular smooth muscle contraction and growth, platelet aggregation, and leukocyte adhesion to the endothelium. Humans with atherosclerosis, diabetes, or hypertension often show impaired NO pathways. A high salt

intake was demonstrated to attenuate NO production in patients with essential hypertension, although bioavailability remains unregulated. Nitric oxide is also generated by phagocytes (monocytes, macrophages, and neutrophils) as part of the human immune response. Phagocytes are armed with inducible nitric oxide synthase (iNOS), which is activated by interferon-gamma (IFN-γ) as a single signal or by tumor necrosis factor (TNF) along with a second signal.

On the other hand, transforming growth factor-beta (TGF-β) provides a strong inhibitory signal to iNOS, whereas interleukin-4 (IL-4) and IL-10 provide weak inhibitory signals. In this way, the immune system may regulate the armamentarium of phagocytes that play a role in inflammation and immune responses. Nitric oxide secreted as an immune response is as free radicals and is toxic to bacteria; the mechanism for this includes DNA damage and degradation of iron sulfur centers into iron ions and iron-nitrosyl compounds.

In response, many bacterial pathogens have evolved mechanisms for nitric oxide resistance. Because nitric oxide might serve as an *inflammometer* in conditions like asthma, there has been increasing interest in the use of exhaled nitric oxide as a breath test in diseases with airway inflammation. Reduced levels of exhaled NO have been associated with exposure to air pollution in cyclists and smokers, but, in general, increased levels of exhaled NO are associated with exposure to air pollution. Nitric oxide can contribute to reperfusion injury when an excessive amount produced during reperfusion (following a period of ischemia) reacts with superoxide to produce the damaging oxidant peroxynitrite. In contrast, inhaled nitric oxide has been shown to help survival and recovery from paraquat poisoning, which produces lung tissue–damaging superoxide and hinders NOS metabolism.

Two important biological reaction mechanisms of nitric oxide are S-nitrosation of thiols, and nitrosylation of transition metal ions. S-nitrosation involves the (reversible) conversion of thiol groups, including cysteine residues in proteins; to form S-nitrosothiols (RSNOs).S-Nitrosation is a mechanism for dynamic, post-translational regulation of most or all major classes of protein. The second mechanism, nitrosylation, involves the binding of NO to a transition metal ion like iron or copper. In this function, NO is referred to as a nitrosyl ligand. Typical cases involve the nitrosylation of heme proteins like cytochromes, thereby disabling the normal enzymatic activity of the enzyme. Nitrosylated ferrous iron is particularly stable, as the binding of the nitrosyl ligand to ferrous iron (Fe (II)) is very strong. Hemoglobin is a prominent example of a heme protein that may be modified by NO by both pathways: NO may attach directly to the heme in the nitrosylation reaction, and independently form S-nitrosothiols by S-nitrosation of the thiol moieties

Effects of Nitric Oxide:

Nitric oxide has major effects that are mediated by activation of cytoplasmic soluble guanylyl cyclase and stimulated production of cGMP, an important second messenger. In addition, nitric oxide can produce several reactive nitrogen derivatives by interaction with molecular oxygen and superoxide radicals. These highly unstable molecules react with a variety of proteins, lipids, nucleic acids, and metals (especially iron) in cells .

Vascular effects:

Nitric oxide has a significant effect on vascular smooth muscle tone and blood pressure. It is released by acetylcholine and other endothelium-dependent vasodilators. It may play a role in the normal regulation of vascular tone as suggested by the fact that a reduction of nitric oxide synthesis (caused by knockout mutations, infusion of NOS inhibitors such as L-NMMA, or by injury to the vascular endothelium) increases vascular tone and elevates mean arterial pressure. The effects of vasopressor drugs are increased by inhibition of NOS. increased cGMP synthesis by guanylyl cyclase results in smooth muscle relaxation. Apart from being a vasodilator, nitric oxide is also a potent inhibitor of neutrophil adhesion to the vascular endothelium. This is due to the inhibitory effect of nitric oxide on the expression of adhesion molecules on the endothelial surface. The role of nitric oxide in protecting the endothelium has been demonstrated by studies that showed that treatment with nitric oxide donors protects against ischemia- and reperfusion-mediated endothelial dysfunction.

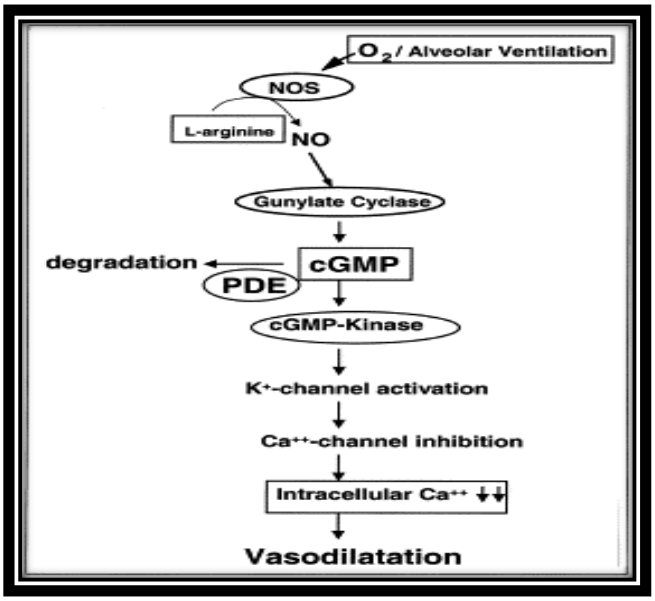
Blood flow:

NO relaxes the smooth muscle in the walls of the arterioles. At each systole, the endothelial cells that line the blood vessels release a puff of NO. This diffuses into the underlying smooth muscle cells causing them to relax and thus permit the surge of blood to pass through easily. Mice whose genes for the NO synthase found in endothelial cells (eNOS) has been "knocked out" suffer from hypertension. Nitroglycerine, which is often prescribed to reduce the pain of angina, does so by generating nitric oxide, which relaxes the walls of the coronary arteries and arterioles.

Vasodilator:

Although the exact mechanisms by which NO produces vasodilatation are not yet defined, it is known that activation of cGMP-dependent protein kinase in smooth muscle cells causes a relaxation of the vessels. Since one of NO's main targets is guanylyl cyclase (which produces cGMP and activates cGMP-dependent protein kinase), it is presumed that one major pathway for NO's vasodilatory actions is through cGMP-dependent protein kinase. Activation of this kinase leads indirectly to decrease Ca^{2+}-levels in the smooth muscle cells and subsequently to the dephosphorylation of the myosin contractile apparatus which causes relaxation. In smooth muscle cells, NO also appears to directly hyperpolarize cells possibly by activating K^{+}-channels, leading to the secondary closure of Ca^{2+} channels which also produces muscle relaxation. In conclusion, one of NO's main functions appears to be integrating the level of neuronal activity with local alterations in cerebral blood flow to maintain adequate perfusion of metabolically active tissue.

Figure-3



Kidney function:

Release of NO around the glomeruli of the kidneys increases blood flow through them thus increases the rate of filtration and urine formation.

Respiratory disorders:

Nitric oxide has been shown to improve cardiopulmonary function in adult patients with pulmonary artery hypertension and is approved for this indication. It is administered by inhalation. It has also been administered by inhalation to newborns with pulmonary hypertension and acute respiratory distress syndrome. The current treatment for severely defective gas exchange in the newborn is with extracorporeal membrane oxygenation (ECMO), which does not directly affect pulmonary vascular pressures. Nitric oxide inhalation decreases pulmonary arterial pressure and improves blood oxygenation. Thus, when pulmonary resistance is elevated, it is possible to exploit the vasodilator properties of nitric oxide by administering it via inhalation of a few parts per million. Adults with respiratory distress syndrome also appear in open trials to benefit from nitric oxide inhalation. Nitric oxide may have an additional role in relaxing airway smooth muscle and thus acting as a bronchodilator. For these reasons, nitric oxide inhalation therapy is being widely tested in both infants and adults with acute respiratory distress syndrome. The adverse effects of this use of nitric oxide are being assessed. Gaseous NO had been explored for use with various cardiovascular, cutaneous vasculature and vascular smooth muscle disorders. Inhaled NO is generally applied at no higher than 80 ppm. Higher concentrations are thought to lead to formation of NO_2, which is known to be a significant irritant in the lungs.

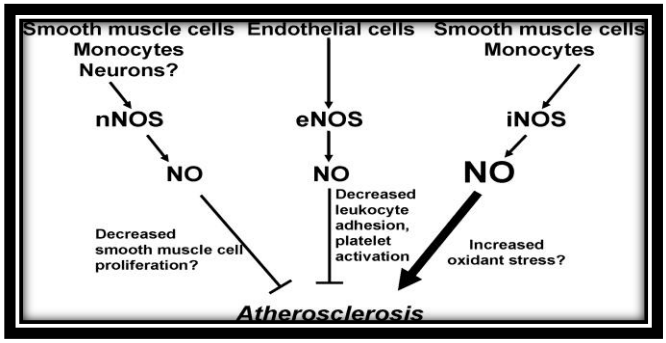
Septic shock:

As mentioned previously, increased urinary excretion of nitrate, the oxidative product of nitric oxide, is reported in gram-negative bacterial infection. Lipopolysaccharide components from the bacterial wall activate the inducible NOS (NOS-2), resulting in exaggerated hypotension, shock, and possible death. This hypotension is reversed by NOS inhibitors such as L-NMMA in humans as well as animal models and by compounds such as methylene blue, which prevent the action of nitric oxide, as well as by scavengers of nitric oxide such as hemoglobin. Furthermore, knockout mice lacking a functional NOS-2 gene are more resistant to endotoxin than wild-type mice. However, there has been no correlation between the hemodynamic effects of the nitric oxide inhibitors and survival rate in gram-negative sepsis thus far.

Atherosclerosis:

Vascular plaque formation in hypercholesterolemia leads to reduced nitric oxide formation and endothelium-dependent vasodilator responses. In vitro, nitric oxide carriers and donors and cGMP analogs inhibit smooth muscle cell proliferation. In animal models, myointimal proliferation following angioplasty can be blocked by feeding arginine, by using nitric oxide donors, by NOS gene transfer, and by nitric oxide inhalation. In addition, nitric oxide may act as an antioxidant, blocking the oxidation of low-density lipoproteins (LDL) and thus preventing the formation of foam cells in the vascular wall.

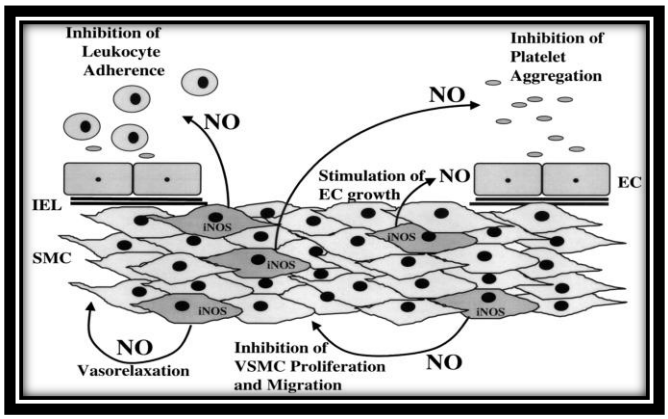
Figure-4



Platelets:

Abnormal activation of platelets is associated with increased platelet adhesion and aggregation and therefore a higher incidence of thrombotic events. Platelet activation also leads to release of smooth muscle mitogens such as growth factors and thromboxane. Nitric oxide is a potent inhibitor of platelet adhesion and aggregation. Thus, endothelial dysfunction and the associated decrease in nitric oxide generation may result in abnormal platelet function. Platelets also contain both constitutive and inducible NOS, although to a much lesser extent than endothelial cells. As in vascular smooth muscle, cGMP mediates the protective effect of nitric oxide in platelets. Nitric oxide may have an additional beneficial effect on blood coagulation by enhancing fibrinolysis via an effect on plasminogen.

Figure-5



Organ transplantation: Accelerated graft atherosclerosis following organ transplantation is a chronic condition and is a major cause of transplant failure, leading to retransplantation or death. Continuous vascular smooth muscle proliferation occurs within the vasculature of most grafts and is a central event in luminal narrowing. Ischemic and reperfusion injuries at the time of organ harvesting, preservation, and revascularization initiate myointimal proliferation, which is also promoted by the continuous immune response to the allogeneic organ graft. By reducing free radical toxicity under these conditions, nitric oxide may act as a cytoprotective agent, inhibiting platelet and neutrophil aggregation and adhesion to the vascular wall. Dietary L-arginine supplementation increases plasma nitrite and nitrate formation and has been shown to attenuate accelerated graft atherosclerosis. However, excessively high concentrations of nitric oxide may be detrimental during *acute* organ rejection due to up-regulation of inducible NOS by cytokines; under these circumstances, *inhibition* of nitric oxide synthesis has been shown to prolong graft survival in experimental animals.

Central nervous system:

Nitric oxide has been proposed to have a major role in the central nervous system—as a neurotransmitter, as a modulator of ligand-gated receptors, or both. In addition, nitric oxide probably plays a role in neuronal degeneration in some conditions. The likely cellular targets of nitric oxide in the central nervous system include presynaptic and postsynaptic nerve terminals. Nitric oxide modifies neurotransmitter release in different areas of the brain. Postsynaptic release of nitric oxide following activation of the NMDA receptor may initiate presynaptic transmitter release of glutamate, ie, nitric oxide may function as a *retrograde* messenger that is synthesized in postsynaptic sites following opening of the Ca2+ channels and activation of NOS. It is proposed that the nitric oxide thus produced rapidly diffuses to the presynaptic nerve terminal where guanylyl cyclase is activated to yield cGMP and thus facilitate transmitter release. In the cerebellum and in neuroblastoma cells, this effect is blocked by NOS inhibitors such as L-NMMA and is enhanced by L-arginine. It has been suggested that nitric oxide (like many other substances) may have a role in short- and long-term potentiating effects on excitatory amino acids in brain development and learning. 7-Nitroindazole, an inhibitor of NOS-1, and L-NAME, a less selective inhibitor of neuronal NOS, have significant antinociceptive effects in humans and animals and 7-nitroindazol reduces the signs of opioid withdrawal and cocaine action in animal models. This inhibitor also reduces cerebral blood flow. Nevertheless, 7-nitroindazole can reduce the size of cerebral infarcts in animal models. In contrast, NOS-3-deficient mice are more susceptible to ischemic cerebral damage. NOS-1 inhibition by 7-nitroindazole also reduces the neurotoxicity of MPTP and MPP+ in several animal models. It is well known that prolonged NMDA glutamate receptor activation results in degeneration of neurons (excitotoxicity). This has been attributed to a large increase in calcium influx, which activates the calmodulin-dependent NOS-1 and leads to sustained elevation of nitric oxide concentrations. The increase in neurodegeneration caused by excitatory amino acids may be due to enhanced oxygen radical formation since superoxide dismutase has a beneficial effect in experimental models. The damage may also be mediated by the generation of secondary radicals such as peroxynitrite, which has a high affinity for sulfhydryl-containing enzymes such as calcium ATPase. Inhibition of calcium ATPases by peroxynitrite may in turn lead to enhanced Ca2+ accumulation and associated neurodegeneration. NOS-2 has been implicated in several other degenerative neurologic conditions, eg, Alzheimer's disease, multiple sclerosis, and Huntington's disease. High levels of nitric oxide have also been shown to cause destruction of photoreceptor cells in the retina. This is believed to be due to a prolonged increase in cGMP formation. Finally, nitric oxide and cGMP have been reported to have a role in epileptic seizures.

Retrograde messenger:

Definition:

Retrograde messenger is a chemical substance that is released from postsynaptic neurons and acts on presynaptic neurons. In the nervous system, information coded by action potentials is transferred from neuron to neuron at a specialized site called "synapse". The transmission at Chemical synapses is generally one-directional.

Neurotransmitters are released from presynaptic terminals on the arrival of action potentials, and transmit a signal to postsynaptic neurons by activating the corresponding receptors. In contrast to this fundamental anterograde information transfer, the signaling from postsynaptic to presynaptic neurons is called retrograde signalling. The retrograde signaling can be mediated by either a diffusible factor that is called "retrograde messenger," or a direct interaction of presynaptic and postsynaptic membrane-bound elements. In typical cases, a retrograde messenger is released from the postsynaptic.

In neuroscience, retrograde signaling (retrograde neurotransmission) is the process by which a retrograde messenger, such as anandamide or nitric oxide, is released by a postsynaptic dendrite or cell body, and travels *backwards* across a chemical synapse to bind to the axon terminal of a presynaptic neuron. The primary purpose of retrograde neurotransmission is regulation of chemical neurotransmission. For this reason, retrograde neurotransmission allows neural circuits to create feedback loops. In the sense that retrograde neurotransmission mainly to regulate typical, anterograde neurotransmission, rather than to actually distribute any information, it is similar to electrical neurotransmission. In contrast with conventional (anterograde) neurotransmitters, retrograde neurotransmitters are synthesized in the postsynaptic neuron, and bind to receptors on the axon terminal of the presynaptic neuron. Endocannabinoids like anandamide are known to act as retrograde messengers, as is nitric oxide. Retrograde signaling may also play a role in long-term potentiation, a proposed mechanism of learning and memory, although this is controversial.

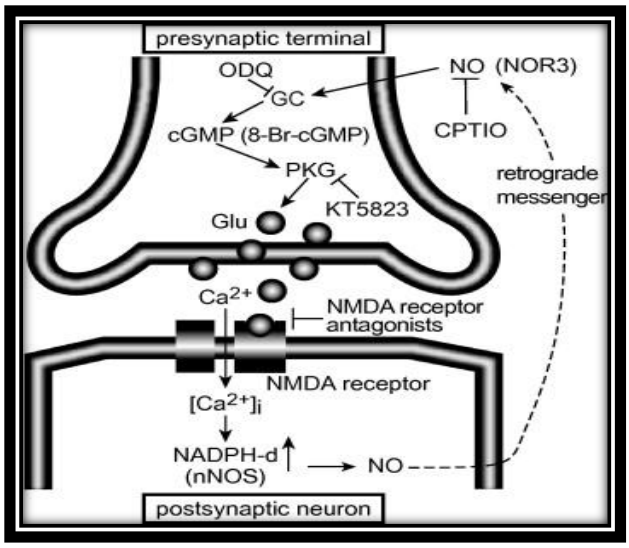
Mechanism:

The retrograde signaling hypothesis proposes that during the early stages of LTP (long-term potentiation) expression, the postsynaptic cell "sends a message" to the presynaptic cell to notify it that an LTP-inducing stimulus has been received postsynaptically. The general hypothesis of retrograde signaling does not propose a precise mechanism by which this message is sent and received. One mechanism may be that the postsynaptic cell synthesizes and releases a retrograde messenger upon receipt of LTP-inducing stimulation. Another is that it releases a preformed retrograde messenger upon such activation. Yet another mechanism is that synapse-spanning proteins may be altered by LTP-inducing stimuli in the postsynaptic cell, and that changes in conformation of these proteins propagate this information across the synapse and to the presynaptic cell.

Identity of the messenger:

Of these mechanisms, the retrograde messenger hypothesis has received the most attention. Among proponents of the model, there is disagreement over the identity of the retrograde messenger. A flurry of work in the early 1990s to demonstrate the existence of a retrograde messenger and to determine its identity generated a list of candidates including carbon monoxide, platelet-activating factor, arachidonic acid, and nitric oxide. Nitric oxide has received a great deal of attention in the past, but has recently been superseded by adhesion proteins that span the synaptic cleft to join the presynaptic and postsynaptic cells. The endocannabinoids anandamide and/ or 2-AG, acting through G-protein coupled cannabinoid receptors, are the primary retrograde messengers in the brain, and may also play an important role in retrograde signaling in LTP. Nitric oxide is the molecule that signals from post synaptic neurons to presynaptic neurons. This causes glutamate release which upregulates presynaptic AMPA receptors thus sustaining long term potentiation.

Figure-6



Peripheral nervous system: Nonadrenergic, noncholinergic (NANC) neurons are widely distributed in peripheral tissues, especially the gastrointestinal and reproductive tracts. Considerable evidence implicates nitric oxide as a mediator of certain NANC actions, and some NANC neurons appear to release nitric oxide. Penile erection is thought to be caused by the release of nitric oxide from NANC neurons; it is well documented that nitric oxide promotes relaxation of the smooth muscle in the corpora cavernosa the initiating factor in penile erection and inhibitors of NOS have been shown to prevent erection caused by pelvic nerve stimulation in the rat. Thus, impotence is a possible clinical indication for the use of a nitric oxide donor, and trials have been carried out with nitroglycerin ointment and the nitroglycerin patch. Another approach is to inhibit the breakdown of cGMP by the phosphodiesterase (PDE isoform 5) present in the smooth muscle of the corpora cavernosa with drugs such as sildenafil.

Penile erection:

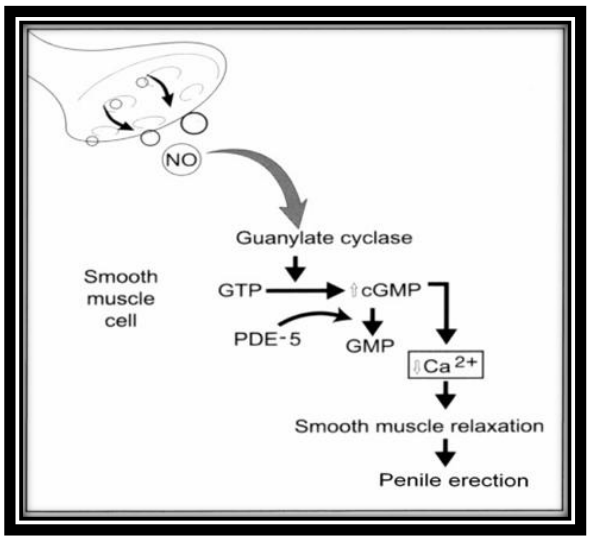
The erection of the penis during sexual excitation is mediated by NO released from nerve endings close to the blood vessels of the penis. Relaxation of these vessels causes blood to pool in the blood sinuses producing an erection.

Three popular prescription drugs

- sildenafil (Viagra®)
- Vardenafil (Levitra®)
- tadalafil (Cialis®)

Enhance this effect by the mechanism described below. Recent evidence suggests that NO's job in reproduction is not finished with producing an erection. At the moment of contact, release of NO by the acrosome of the sperm activates the egg to complete meiosis II and the other steps of fertilization.

Figure-7



Inflammation:

Nitric oxide has a role in both acute and chronic inflammation. NOS-3 is involved in the vasodilation associated with acute inflammation. In experimental models of acute inflammation, inhibitors of NOS-3 have a dose-dependent protective effect, suggesting that nitric oxide promotes edema and vascular permeability. Nitric oxide has a detrimental effect in chronic models of arthritis; dietary L-arginine supplementation exacerbates arthritis whereas protection is seen with NOS-2 inhibitors. Psoriasis lesions, airway epithelium in asthma, and inflammatory bowel lesions in humans all demonstrate elevated levels of nitric oxide and NOS-2. Synovial fluid from patients with arthritis contains increased oxidation products of nitric oxide, particularly peroxynitrite. Recent studies have shown that nitric oxide stimulates the synthesis of inflammatory prostaglandins by activating cyclooxygenase isoenzyme II (COX-2). Thus, inhibition of the nitric oxide pathway may have a beneficial effect on inflammatory diseases, including joint diseases. Studies using inhibitors of NOS-2 have shown that nitric oxide is required for maintaining COX-2 gene expression. Nitric oxide also appears to play an important protective role in the body via immune cell function. When challenged with foreign antigens, TH1 cells respond by synthesizing nitric oxide. Inhibition of NOS and knockout of the NOS-2 gene can markedly impair the protective response to injected parasites in animal models.

Other Actions on Smooth Muscle: [17-21]

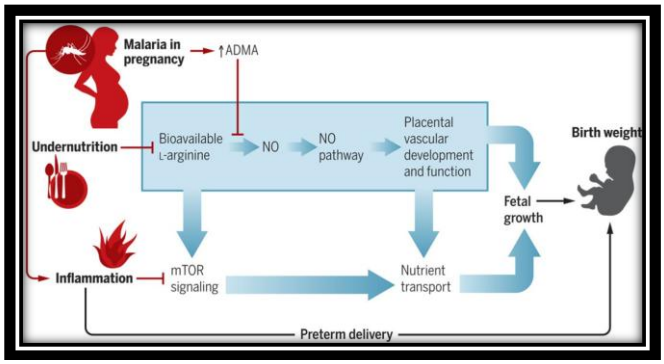
Peristalsis:

The wavelike motions of the gastrointestinal tract are aided by the relaxing effect of NO on the smooth muscle in its walls.

Birth:

NO also inhibits the contractility of the smooth muscle wall of the uterus. As the moment of birth approaches, the production of NO decreases. Nitroglycerine has helped some women who were at risk of giving birth prematurely to carry their baby to full term. Nitric oxide also help full for fetal growth and weight in condition of malaria in pregnancy, nutrition deficiency and during inflammatory conditions.

Figure-8



Effects on secretion:

NO affects secretion from several endocrine glands.

For examples, it stimulates

- The release of Gonadotropin-releasing hormone (GnRH) from the hypothalamus,
- The release of pancreatic amylase from the exocrine portion of the pancreas,
- The release of adrenaline from the adrenal medulla.

NO and the autonomic nervous system

Some motor neurons of the parasympathetic branch of the autonomic nervous system release NO as their neurotransmitter. The actions of NO on penile erection and peristalsis are probably mediated by these nerves.

NO and the medulla oblongata:

Hemoglobin transports NO at the same time it carries oxygen. When it unloads oxygen in the tissues, it also unloads NO. In severe deoxygenation, NO-sensitive cells in the medulla oblongata respond to this release by increasing the rate and depth of breathing.

NO and the brain (Nitric Oxide Helping the Brain):

Nitric oxide is distributed throughout the brain and may have an involvement in almost all of its normal physiological functions. A cell in the brain is responsible for releasing a chemical messenger called glutamate, which stimulates another cell, a receptor cell, with this chemical to release nitric oxide. If it is strongly stimulated, the receptor sends back a nitric oxide molecule to tell the sender that the message was received, and asks it to send an even stronger message next time. In laboratory animals (mice and rats), NO is released by neurons in the CA1 region of the hippocampus and stimulates the NMDA receptors there that are responsible for long-term potentiation (LTP) ,a type of memory (and learning).

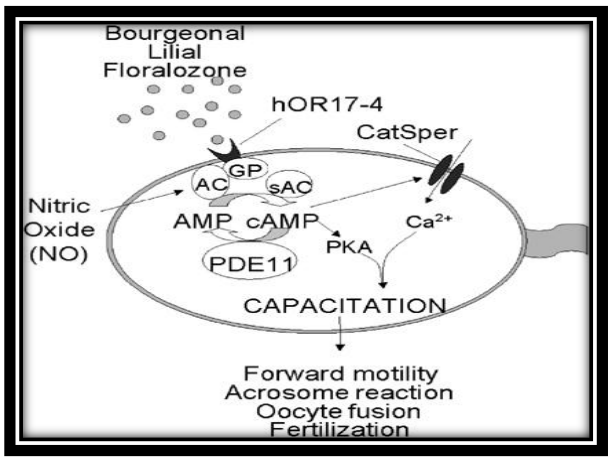
The ease with which NO diffuses away from the synapse where it is generated enables it to affect nearby synapses. So what may have begun as a localized action becomes magnified. Laboratory rats treated with inhibitors of NOS synthesis fail to develop and/or retain learned responses such as the conditioned response. Mice whose genes for nNOS have been knocked out are healthy but display abnormal behavior, e.g., they kill other males and try to mate with nonreceptive females.

***NO and fertilization*:** The acrosome at the tip of sperm heads activates it's NO synthase when it enters the egg. The resulting release of NO in the egg is essential (at least in sea urchins) for triggering the next steps in the process:

*blocking the entry of additional sperm and

*orienting the pronuclei for fusion.

Figure-9



Killing pathogens: NO aids in the killing of engulfed pathogens (e.g., bacteria) within the lysosomes of macrophages. Mice whose genes for the NO synthase found in macrophages (iNOS) have been knocked out are more susceptible to infections by intracellular bacteria like Listeria monocytogenes. Th1 cells, the ones responsible for an inflammatory response against invaders, secrete NO. Harmless bacteria, living as commences at the rear of our throat, convert nitrates in our food into nitrites. When these reach the stomach, the acidic gastric juice (pH~1.4) generates NO from them. This NO kills almost all the bacteria that have been swallowed in our food. (Since the dawn of recorded human history, nitrites have been used to preserve meat from bacterial spoilage.)

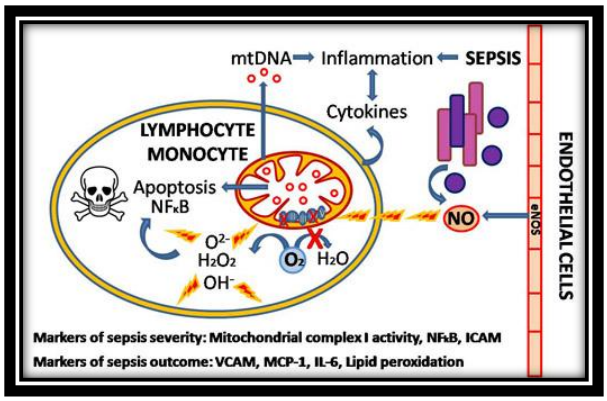
NO and longevity:

Mice whose genes for eNos have been knocked out Show signs of premature aging, Have a shortened life span, Fail to benefit from the life-extending effect of a calorie-restricted (CR) diet.

Immune system:

Macrophages, certain cells of the immune system, produce nitric oxide in order to kill invading bacteria. In this case, the nitric oxide synthase is inducible NOS. Under certain conditions, this can backfire: Fulminant infection (sepsis) causes excess production of nitric oxide by macrophages, leading to vasodilatation (widening of blood vessels), probably one of the main causes of hypotension (low blood pressure) in sepsis. The inducible isoform of nitric oxide synthase is expressed and produces cytotoxic levels of nitric oxide.

Figure-10



Neurotransmission:

Nitric oxide also serves as a neurotransmitter between nerve cells, part of its general role in redox signaling. Unlike most other neurotransmitters that only transmit information from a presynaptic to a postsynaptic neuron, the small, uncharged, and fat-soluble nitric oxide molecule can diffuse widely and readily enters cells. Thus, it can act on several nearby neurons, even on those not connected by a synapse. At the same time, the short half-life of NO means that such action will be restricted to a limited area, without the necessity for enzymatic breakdown or cellular reuptake. NO is also highly reactive with other free radicals, lipids, and proteins. NO-cGMP cascade is involved in learning and memory through the maintenance of long-term potentiation (LTP). Nitric oxide is an important non-adrenergic, non-cholinergic (NANC) neurotransmitter in various parts of the gastrointestinal tract. It causes relaxation of the gastrointestinal smooth muscle. In the stomach it increases the capacity of the fundus to store food and fluids.

Neuromodulator:

NO is also thought to act as a locally diffusible messenger. It is produced by any action that elevates Ca^{2+} in cells containing NOS, such as glutamate stimulation of NMDA receptors. Through subsequent activation of guanylyl cyclase and production of cGMP, NO production influences a variety of secondary processes. These include direct modulation of ion channels, stimulation of cGMP-dependent protein kinase, and both up-regulation or down-regulation of cAMP-phosphodiesterase. Downstream effects are then numerous and include up and down regulation of Ca^{2+} channels, increased excitability (increases neuronal firing rate), increased or decreased neurotransmitter release, and changes in neuron morphology.

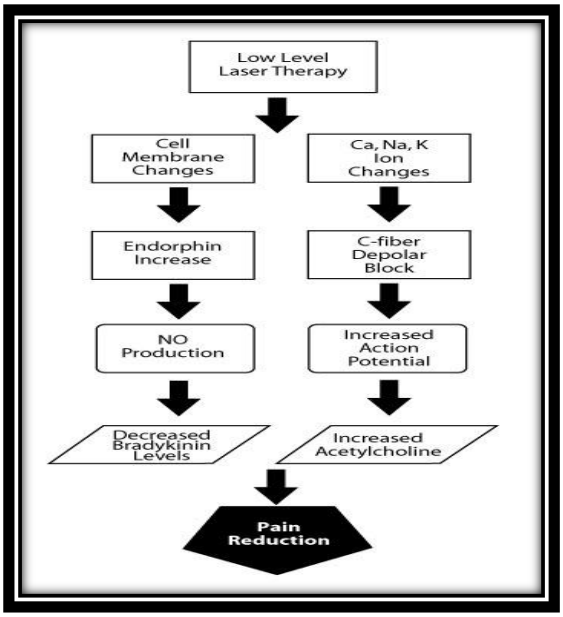
Blood circulation (High blood pressure):

One of nitric oxide's best known functions is as a regulator of blood pressure. In a process referred to as vasodilation, nitric oxide relaxes and widens blood vessels, which improves blood flow and prevents clotting. Nitric oxide accomplishes this by spreading from the innermost cell layer of the arteries to their underlying muscle cells. Nitric oxide prevents these cells from contracting, leaving them relaxed and dilated. Through the extracts of the noni tree, nitric oxide can be a useful adjunct to help millions of people in normalizing their blood pressure along with a healthy diet and exercise.

Nitric oxide helps to reduce pain:

Nitric oxide helps reduce pain, when many drugs are being prescribed for pain relief. Scientific research shows that the pain-relieving effects of medications like morphine, aspirin, and oxytocin are due to the release of nitric oxide.

Figure-11



Nitric oxide helps with weight loss:

Inside the cells of the body are tiny mitochondria, the places where food and oxygen are turned into energy. The mitochondria is where all fat is burned, in addition to generating almost all of a person's energy used and controlling cellular metabolism. Research is showing that nitric oxide not only stimulates the creation of new mitochondria, but also may make each individual mitochondrion larger, which helps burn even more fat and therefore could result in weight loss.

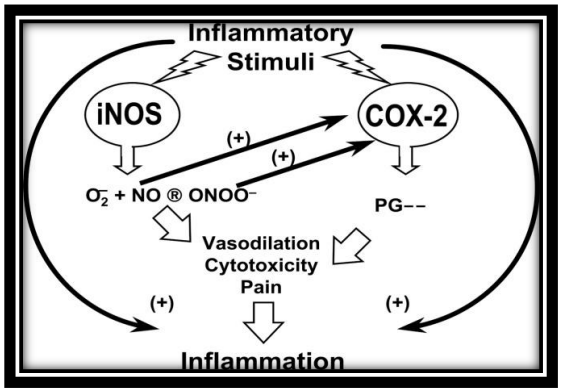
Nitric oxide increases energy:

Exercise increases nitric oxide and taking a substance that increases nitric oxide increases the energy to exercise

Nitric oxide reduces inflammation:

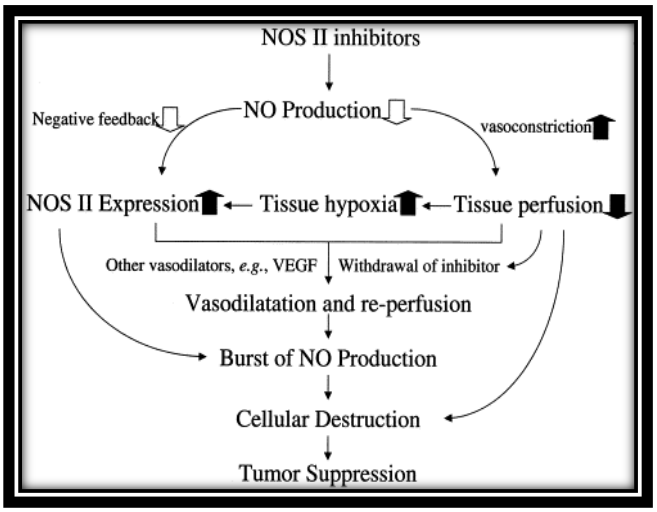
Nitric oxide inhibits inflammation in blood vessels by blocking the inflammation that occurs in damaged endothelial cells. If these cells become damaged or dysfunctional, nitric oxide production become impaired, this leads to more inflammation and tissue damage.

Figure-12



Nitric oxide and the prevention of cancer: White blood cells, use nitric oxide to defend against cancerous tumors. Several studies show nitric oxide can inhibit cancer cells.

Figure-13



Nitri oxide improves digestion:

Nitric oxide is heavily involved in the processes of the digestive tract. Nitric oxide regulates blood flow to the gut, which helps you digest food and keeps the lining of the gut undamaged to protect from invaders. It also actively is able to kill off those invaders.

Other functions:

Dietary nitrate is also an important source of nitric oxide in mammals. Green, leafy vegetables, and some root vegetables (such as beetroot) have high concentrations of nitrate. When eaten and absorbed into the bloodstream nitrate is concentrated in saliva (about 10 fold) and is reduced to nitrite on the surface of the tongue by a biofilm of commensally facultative anaerobic bacteria. This nitrite is swallowed and reacts with acid and reducing substances in the stomach (such as ascorbate) to produce high concentrations of nitric oxide. The purpose of this mechanism to create NO is thought to be both sterilization of swallowed food, to prevent food poisoning and to maintain gastric mucosal blood flow.

A similar mechanism is thought to protect the skin from fungal infections, where nitrate in sweat is reduced to nitrite by skin commensal organisms and then to NO on the slightly acidic skin surface. Alternatively, nitrite anions on sun-exposed skin may be photolyzed to free nitric oxide radicals by UVA in sunlight. This mechanism may elicit significant changes to the systemic blood circulation in humans and exploited for therapeutic purposes.

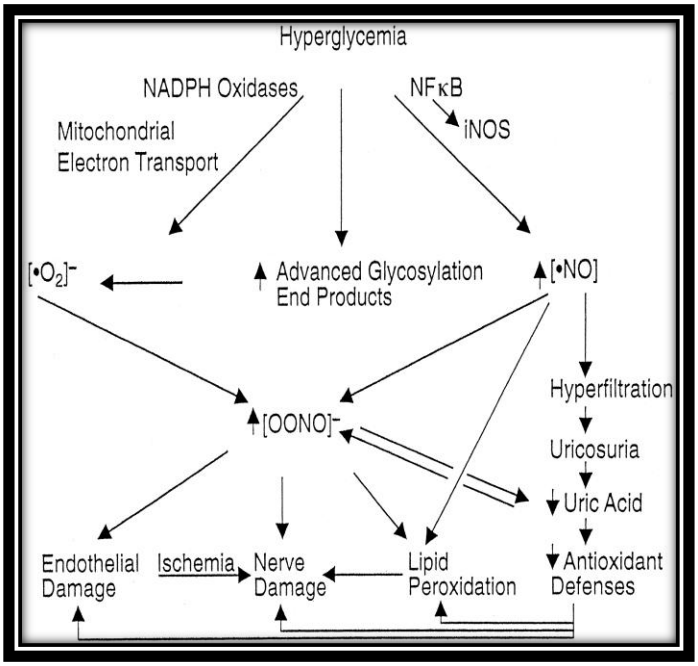
Nitric oxide also acts on cardiac muscle to decrease contractility and heart rate. NO contributes to the regulation of cardiac contractility. Emerging evidence suggests that coronary artery disease (CAD) is related to defects in generation or action of NO. Reduced levels of exhaled NO have been associated with exposure to traffic related air pollution. The bacterium *Deinococcus radiodurans* can withstand extreme levels of radioactivity and other stresses. In 2009 it was reported that nitric oxide plays an important role in this bacteria's recovery from radiation exposure: the gas is required for division and proliferation after DNA damage has been repaired. A gene was described that increases nitric oxide production after UV radiation, and in the absence of this gene the bacteria were still able to repair DNA damage, but wouldn't grow.

Pathology:

People with diabetes usually have lower levels of nitric oxide than patients without diabetes. Diminished supply of nitric oxide can lead to vascular damage, such as endothelial dysfunction and vascular inflammation. Vascular damage can lead to decreased blood flow to the extremities, causing the diabetic patient to be more likely to develop Neuropathy, non healing ulcers, and to be at a greater risk for lower limb amputation.

Pharmaceutical analogs : Nitroglycerin, amyl nitrite, "poppers" (isobutyl nitrite or similar), and other nitrite derivatives are used in the treatment of heart disease: The compounds are converted to nitric oxide (by a process that is not completely understood), which in turn dilates the coronary artery(blood vessels around the heart), thereby increasing its blood supply. These drugs, however, are predominantly venodilators, dilating peripheral veins and hence reducing venous return and preload to the heart. This reduces the oxygen requirement of the myocardium and subsequently lessens the anginal pain felt with myocardial ischemia.

Figure-14



Medical Use:

Neonatal use:

Nitric oxide/oxygen blends are used in critical care to promote capillary and pulmonary dilation to treat primary pulmonary hypertensionin neonatal patients post-meconium aspiration and related to birth defects. These are often a last-resort gas mixture before the use of extracorporeal membrane oxygenation (ECMO). Nitric oxide therapy has the potential to significantly increase the quality of life and, in some cases, save the lives of infants at risk for pulmonary vascular disease.

Pediatric and adult use:

Currently in the United States, nitric oxide use is not approved for any population other than neonates. In the adult

ICU setting, inhaled NO can improve hypoxemia in acute lung injury, acute respiratory distress syndrome, and severe pulmonary hypertension, although the effects are short-lived and there are no studies demonstrating improved clinical outcomes. It is used on an individualized basis in ICUs as an adjunct to other definitive therapies for reversible causes of hypoxemic respiratory distress.

Dosage and strength:

Currently in the United States, nitric oxide is a gas available in concentrations of only 100 ppm and 800ppm.Overdosage with inhaled nitric oxide will be seen by elevations in methemoglobin and pulmonary toxicities associated with inspired NO2. Elevated NO2 may cause acute lung injury.

Contraindications:

Inhaled nitric oxide is contraindicated in the treatment of neonates known to be dependent on right-to-left shunting of blood.

Associated problems:

There are some associated complaints with utilization of nitric oxide in neonatal patients. Some of them include dose errors associated with the delivery system, headaches associated with environmental exposure of nitric oxide in hospital staff, hypotension associated with acute withdrawal of the drug, hypoxemia associated with acute withdrawal of the drug, and pulmonary edema in patients with CREST syndrome.

Preparations Available:

Nitric Oxide (INOmax): Inhalation: 100, 800 ppm gas

Effects on plants:

In plants, nitric oxide can be produced by any of four routes:

(i) L-arginine-dependent nitric oxide synthase, (although the existence of animal NOS homologs in plants is debated),

(ii) plasma membrane-bound nitrate reductase,

(iii) mitochondrial electron transport chain, or

(iv) non-enzymatic reactions. It is a signaling molecule, acts mainly against oxidative stress and also plays a role in plant pathogen interactions.

Treating cut flowers and other plants with nitric oxide has been shown to lengthen the time before wilting. Numerous important discoveries about nitric oxide function within plants starting in the 1990's have made it clear that nitric oxide is an important signaling compound in plants. It is involved in such diverse functions as regulation of defense mechanisms in plant-pathogen interaction, promotion of the plant hypersensitive response, symbiosis (for example, with organisms in nitrogen-fixing root nodules), development of lateral and adventitious roots and root hairs, and control of stomatal opening. Nitric oxide is known to be produced by cellular organelles, including mitochondria, peroxisomes, and chloroplasts. It plays a role in antioxidant and reactive oxygen species responses. Nitric oxide interactions have been found within signaling pathways of important plant hormones such as auxin and cytokinin. These recent discoveries are stimulating new research into nitric oxide's role within plants [22-24].

CONCLUSION

In this review of literature, nitric oxide has been shown to have diverse biological functions and effects within the immune system and also it plays a key role in both physiologically and pathologically. Within the scope and limitations of this review, only a brief overview could be given on nitric oxide. It covers more information that it would be beneficial to dissect the research down much further. Further informative research into the fascinating nitric oxide molecule shall no doubt be only a short time away.

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