The Magical Wonders of Nitric Oxide: The Molecule of the Millennium

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ABSTRACT

NO is a gas and has a very short half-life (3-5s), as it is highly reactive. No and its products are inactivated through oxidation into nitrite (NO₂⁻) and nitrate (NO₃⁻) Which is excreted in the urine. NO is regarded as magical molecule which has profound role in regulation of various function in various organs of human body and in health and disease. Here in this review article authors has discussed about its chemistry and metabolism, its discovery, its basic functions, role in pathophysiology of various diseases and its therapeutic implications.

Key Words: NO, eNOS, EDRF,

INTRODUCTION

Chemistry and Metabolism: NO is a gas and has a very short half-life (3-5s), as it is highly reactive. No and its products are inactivated through oxidation into nitrite (NO₂⁻) and nitrate (NO₃⁻) Which is excreted in the urine [1]. The Plasma and urine concentrations of NO₃⁻ and cGMP are useful indicators for turnover of NO i.e. its production and excretion [2].

Discovery: An unexpected and exciting discovery was made that relaxation of isolated preparations of rabbit aorta by acetylcholine was eliminated if the intimal surface of preparations was rubbed prior to testing with acetylcholine (Rubbing damaged the endothelium lining cells). This showed that the relaxation by Acetylcholine was not the result of a direct action on the arterial smooth muscle but rather of an indirect action in which Ach acted on muscarinic receptors of the endothelial cells, stimulating these cells to release a factor that in turn acted on the smooth muscle cells to cause relaxation. The relaxing factor was referred to as Endothelium derive Relaxing Factor (EDRF) [3]. Relaxation of arteries by acetylcholine is endothelium dependent [4]. The discovery of the NO – dependent vasodilator tone indicated the existence of an endogenous vasodilator system, the actions of which are imitated by compounds such as glyceryl tri-nitrate and sodium nitroprusside [5, 6].

Synthesis of NO: NO is synthesized from arginine in a reaction catalyzed by nitric oxide
syntheses (NOS) Figure 1. Three isoforms of NOS have been identified. NOS 1 is found in the nervous system, NOS 2 is found in macrophages and other immune cells. And NOS 3 (e-NOS) is found in endothelial cells. NOS 1 and NOS 3 are activated by agents that increase intracellular Ca++ concentration, including the vasodilators acetylcholine and bradykinin. The NOS in immune cells is not induced by Ca++ but is activated by cytokines. NO is synthesized from arginine in endothelial cells and its action via stimulation of soluble guanyl cyclase and generation of cGMP to produce relaxation in vascular smooth muscle cells. The endothelial form of Nitric oxygen Synthase (NOS) is activated by increased intracellular CA++ Concentration, and an increase is produced by acetylcholine (Ach), Bradykinin or shear stress acting on the cell membrane. Thiol, tetrahydrobiopterin, FAD and FMN are the requisite cofactors [7].

E-NOS (usually referred as eNOS): Originally (e-NOS) characterized in aortic endothelium, now is known to be expressed in cardiac myocytes [8], blood platelets [9], hippocampal neurons [10], pulmonary epithelium [11], renal epithelium [12] and other tissues. In the vascular wall eNOS, plays a key role in vasodilation, and may also regulated vascular smooth muscle cell proliferation, platelet adherence and activation, Leucocyte adherence and chemokine production. In cardiac myocytes, eNOS play a key role in the modulation of autoimmun control of contractility and heart rate. Endothelial NOS (eNOS) knock out mice are Hypertensive and lack EDRF activity [13].

Functions of NO

NO in Vascular homeostasis: When flow to a tissue is suddenly increased by arteriolar dilation large arteries to the tissue also dilate. The flow-induced dilation is due to local release of NO is termed as post stenotic vasodilation [14] products of platelet aggregation also cause release of NO, and the resulting vasodilation helps keep blood vessels, within an intact endothelium patent. This is in contrast to injured blood vessels, where the endothelium is damaged at the site of injury and platelets therefore aggregate and produce vasoconstriction. NO relaxes vascular smooth muscle cells. NO interferes with the secretion and action of endothelium, a potent vasoconstrictor. These seems to be a balance between endothelium derived vasoconstrictors and vasodilators for normal orderly for of blood.

NO in penile erection: There is good evidence to suggest that penile erection is produced by release of NO with consequent vasodilation and engorgement of the corpora cavernosa inhibitor of cGMP- specific phosphodiesterase acts by inhibiting the inactivation of NO [15].

NO as a neurotransmitter: NO is produced in the brain and is responsible for long term potentiation- LTE and long term depression 16. In the cerebellum NO is inhibitory and in the hippocampus NO is stimulatory and plays a role in learning and memory. Simultaneous firing of climbing and parallel fibers in Purkinje fiber.

Other Function of NO: NO is necessary for the cytotoxic activity of macrophages, including their ability to kill cancer cells.

Role of NO in Pathophysiology of Diseases

No in Hypertension: When various derivatives of arginine are administered to experimental animals, there is a prompt rise in blood pressure. This suggests that tonic release of NO is necessary to maintain blood pressure. Impaired production of NO has been implicated in several cardiovascular disorders, including Hypertension, vasospasm and atherosclerosis [17]. Elevated Blood pressure is a common condition that may lead
to well defined complications including stroke, congestive heart failure. In addition, Hypertension is a well-known risk factor for development of atherosclerosis. The vast majority of Hypertensive patients have no apparent cause for their elevated blood pressure called essential hypertension. In humans with essential hypertension there is increasing of NO [18]. Other action of NO that relate to the cardiovascular system include inhibition of white cell activation and inhibition of smooth muscle cell proliferation [17, 19]

**NO: The Antiatherogenic molecule:** Nitroglycerin & other nitro vasodilators that are of great value in the treatment of angina act by stimulating guanylylcyclase in the same manner as NO does. NO decreases LDL oxidation and inhibits superoxide (O$_{2}^{-}$) production by inhibiting NADP reductase activity. These actions are related to the strong “antiatherosclerotic effets” of NO.

Some of the critical events involved in atherogenesis are monocyte adherence and infiltration, plalet adherence and aggregation, and proliferation of vascular smooth muscle cells. EDENO has been shown to inhibit each of these end thus NO is an endogeneous and anti-atherogenic molecule [20-21].

**NO and Vascular Inflammation:** In addition to its vasodilator actions, NO also contributes to the control of platelet aggregation and the regulation of cardiac contractility. These physiological effects of NO are all mediated by activation of soluble guanylate. NO now is also known to be the mediator released in the peripheral nervous system by a widespread network of nerves, previously recognized as noradrenergic and no cholinergic [22]. Evidence suggests that tonic influence of vasodilator nerves is essential for the maintenance of blood supply to brain regions [23].

**NO and Pulmonary Hypertension:** More than a century ago [24] it was observed that acute alveolar hypoxia produces pulmonary vasoconstriction. Evidence in favor of a role of NO in limiting hypoxic vasoconstriction has come from experiments in isolated rat lungs in which inhibitors of NO activity or NO synthesis [25]. The pulmonary vasodilator effect of inhaled NO is not accompanied by systemic hypotension, as NO that diffuses into bloodstream is inactivated by binding to hemoglobin 26. NO appears to be important in the regulation of basal pulmonary vascular tone, in mediating the transition from the fetal to the neonatal circulation, in modulating the pulmonary vasoconstriction associated with acute hypoxia and in limiting the pulmonary vascular remodeling that occurs in chronic hypoxia. Inhaled NO has been shown to decrease pulmonary Hypertension selectively in a variety of clinical settings.

Further advances may include improving pulmonary vascular remodeling in chronic forms of pulmonary hypertension by long-term administration of NO, NO donors, and/or PDE inhibitor.

**Therapeutics Implications**

**Heart Failure:** Studies of Arginine in patients with chronic heart failure have shown mixed results. Some studies report improved exercise tolerance. There is evidence from several studies that arginine taken by mouth or by injection improves exercise tolerance and blood flow in arteries of the heart. Benefits have been shown in some patients with coronary artery disease and angina. Further research is needed to establish doses that are safe and effective and to compare Arginine with prescription drugs used for the same purposes. However additional studies are needed.

**Peripheral Vascular Disease, Claudication:** Intermittent claudication is the
Leg pain and fatigue that occur with exercise of some people with clots in arteries in their legs. A small number of studies suggest that arginine therapy may improve walking distance; Further research is needed before a strong recommendation can be made [28].

**Erectile Dysfunction:** With the emerging body of evidence indicating the involvement of the NO pathway in multiple aspects of the penile erectile response, the use of L-arginine supplementation is a promising therapy in erectile dysfunction. Early studies suggest that men with low nitrate or nitrite levels in their urine may find arginine supplements useful for treating erectile dysfunction in aged smokers [28], diabetes [29], hypertension, atherosclerosis [30] and hypogonadism [31] that are associated with reduced production of EDNO. However, it is not clear what doses may be safe and effective in treating this condition.

**Hormone Therapy:** In postmenopausal women, estrogen improves coronary and systemic endothelium dependent vasomotor responsiveness; an effect associated with increased NO bioactivity [32].

**Future Strategies**

There are a number of ways of augmenting NO levels locally including the use of authentic NO either as an inhaled gas or as a dissolved gas in solution, organic NO donors, infusion or diet supplementation with L-arginine or BH4 or its analogues, NOS gene transfer.

**Arginine:** NO donor arginine has been suggested as a treatment for many conditions, There is supporting evidence that the use of arginine in treating some heart and vascular conditions, erectile dysfunction and migraine headache pain 33 ,improving recovery after operation There is not enough evidence for the support of use in medical conditions and research is underway in this direction for future therapeutic implications of NO. Accumulating evidence indicates that supplemental administration of L-arginine is sufficient to restore EDNO production in which EDNO is reduced. Scientists have studied arginine (also known as L-arginine) for the above clinical problems 34.

The development of methods of practical L-arginine delivery in the quantities required will likely accelerate in acceptance in routine clinical practice example in erectile dysfunction, coronary artery disease and interstitial cystitis.

**Nitrate:** Nitroglycerine and organic nitrate continue to play a significant beneficial role in cardiovascular medicine. These agents are useful to all of the ischemic cardiac syndromes, usually as adjunctive therapy. There is no better therapy. For treatment of acute episodes of anginal pain or unstable angina. If the corundum of nitrate tolerance can be resolved’ nitrates should enjoy an even larger place as part of our therapeutic Armamentarium [35].

**Antioxidants:** Endothelium dependent vasodilation is impaired in most if not all the factors associated with atherosclerosis. Antioxidants improve endothelium dependent vasodilation in patients with coronary atherosclerosis. Antioxidant therapies also restore endothelium dependent vasodilation in patients with diabetes, hypercholesterolemia, and hypertension and in smokers. Thus, inactivation of NO by oxygen-derived free radicals may be a theme common to atherosclerosis and its risk factors. Antioxidant therapy by improving the bioavailability of NO [36], may not only improve vasomotor function and subsequently reduced adverse cardiovascular events in patients with atherosclerosis, but also has the potential to retard atherogenesis in patients for atherosclerosis.
**NO Donors and their Usefulness:** There are a wide variety of nitrogenous compounds that can release NO in solution. These NO generating compounds are collectively known as NO donors. The major classes of organic NO donors are syndnonimines (SIN-1), cysteine-containing NO donors (SPM-5185), the nitrates known as organic nitrates widely used for many years (e.g. Nitroglycerine, sodium nitroprusside)[37].

NO is cytoprotective (suppresses endothelial leucocyte interaction) in reperfusion injury. NO donors have been used to reduce platelet deposition and intimal proliferation following angioplasty. By preventing early platelet attachment and activation to the thrombogenic surface, a S-nitrosated albumin coating may reduce the incidence of acute thrombosis and restenosis following angioplasty [38].

**NOS Inhibitors & Gene Therapy:** Another approach to study the effects of NO in ischemia reperfusion is to inhibit its synthesis by use of inhibitors of NOS. However, detrimental effects have been reported with use of NOS inhibitors as they also have their own direct affects on the vasculature for example contractile dysfunction after the use of L-NAME. Given to the recent rapid progress in technology development and gene therapy the approach of NO gene therapy in areas of cardiovascular disease e.g. using NOS over expression in atherosclerosis & Prinzmetal angina & inhibition of NOS in septicemia induced vasodilation will almost certainly bring new benefits to treatment of these diseases [39].

**REFERENCES**


