NITRIC OXIDE – A UBIQUITOUS BIOMEDIATOR

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Summary

Nitric oxide is a free radical, and its omnipresence in all tissues reveals its versatile nature of being involved in all physiological functions. It has been recognized to play key role in many physiological functions like vascular tone, inhibition of platelet aggregation, cell adhesion, neurotransmission, penile erection and enzyme and immune regulation. In this review, an effort is being made to track its role in physiological and pathophysiological conditions.

Key Words: Endothelium derived-relaxing factor, Ntric oxide, Biomediator

Introduction

Since the discovery of endothelium derived-relaxing factor (EDRF) (1) and its subsequent identification as nitric oxide (NO), (2) the research in the field of biological sciences has never remained the same. This finding, the long awaiting breakthrough, has revolutionized and broadened the horizons of biosciences. NO is a free radical and serves as an important intercellular mediator implicated in a wide range of biological functions like control of vascular tone, platelet aggregation, cell adhesion, neurotransmission, penile erection and enzyme and immune regulation.(3)(4)

NO is biosynthesized from the amino acid L-arginine by an enzyme nitric oxide synthase (NOS). (5) Mammalian NO synthesis is mediated by at least three NOS isoforms; endothelial NOS (eNOS), neuronal NOS (nNOS) and inducible NOS (iNOS).(6)(7) All these NOS isoforms have been cloned and expressed from human cells.(8)

Physicochemical Properties

NO in the pure state under standard temperature and pressure is a gas. With the exception of the lung (e.g., in the presence of a gaseous phase), NO acts as a dissolved nonelectrolyte in all its biological activities. Thus virtually in all biologically relevant conditions NO is not a gas.(4) Studies have suggested that, NO is unstable with an apparent half life of 6-60 seconds and does not persist as the $NO^{\cdot}$ moiety for any length of time owing to reactions with oxygen or super oxide anion (O_2^-). The addition of NO to an aqueous saline environment under physiological conditions of temperature, oxygen tension and pH results in accumulation of nitrite (NO_2^- and lesser amounts of nitrate (NO^-_3)). It should be noted that the interaction of NO with oxygen has the potential to generate additional higher oxides of nitrogen, including NO_2, N_2O_3 and N_2O_4 which will be produced *in vivo* only under pathological conditions in which high concentrations of NO can be generated locally would express activities and toxicities independently of NO.(9)

Biological Chemistry (9)

The biological actions of NO are dictated by the reactions it undergoes with target molecule in cells, membranes and the extra cellular milieu. Apart from being relatively stable free radical gas, it is its propensity to undergo electron transfer reactions or addition reactions with particular molecules, especially those having unpaired electrons (i.e., a free radical) that make its behavior in biological setup interesting. Thus in biological systems, the dominant reactions of NO will be with another free radical such as super oxide anion (O_2^-), a transition metal (e.g., heme iron), or oxygen. These NO adducts, their secondary reaction products and products of NO oxidation and reduction are capable of reacting with metals, thiols and additional target to give further products often with biological activity and relevance.

NO in Vascular tone

NO contributes to the complex regulation of local and systemic vascular resistance, distribution of blood flow and oxygen delivery, sodium balance and arterial pressure. NO diffuses from endothelial cell, where it is synthesized by eNOS, to the adjacent vascular smooth muscle cells, activating soluble guanylate cyclase (sGC), producing cyclic guanosine monophosphate (cGMP), that then mediates further signal transduction ultimately leading to vasorelaxation.(10) Mechanical stimuli such as shear stress are also sufficient to evoke changes in intracellular calcium and NO synthesis which may act to minimize cardiac load by optimally dilating local systemic vasculature.(11) Endothelial dysfunction augments pressor responses and cause hypertension. Cyclosporine, an immunosuppressant, leads to both systemic hypertension and renal vasoconstriction owing to its toxicity on endothelial cells.(12)

NO in Inhibition of Platelet Aggregation

In addition to its vasorelaxant activity, NO also inhibits platelet aggregation via the sGC-cGMP dependant pathway.

Together with prostacyclin, NO acts synergistically to inhibit platelet aggregation and to disaggregate platelets possessing superior antithrombatic effect.(13) NO also inhibits platelets adhesion to collagen fibrils, endothelial cell matrix and endothelial cell monolayers.(14) Recently it has become clear that, platelets also generate NO and that the L-aginine-NO pathway acts as a negative feed back mechanism to regulate platelet aggregation.(15) As a modulator in inhibition of platelet aggregation and vasodilatation, NO can regulate cardiac load at a local level, thereby acting as an important autocrine homeostatic modulator for the vascular system.(4)

NO in Immune System

NO produced in macrophages by iNOS isoform, which is unique that its activity is independent of intracellular Ca^{2+} levels, is found to play a role in host defense mechanism as it has been shown to be cytotoxic or cytostatic for tumor cells and invasive organisms. The stimulation for NO synthesis is brought about by various inflammatory stimuli and agents like lipopolysaccharide, Bacillus Calmette Guerin (BCG), interferon-τ and tissue necrosis factor (TNF).(16) Recent studies have been demonstrated that NO synthesis can be induced in neutrophils, T-lymphocytes, Kupffer cells and hepatocytes.(15)(17)(18) NO synthesis by activated macrophages results in nitrogen oxide species which are more reactive than NO, and play a role in immune system induced cell and tissue damage.(19)

NO in Neurotransmission

The brain contains by far the highest activity of NOS of any tissue so far examined and the widespread enzyme therein indicates that NO could be involved in practically all aspects of CNS function. Synthesized by nNOS in neurons, NO is released upon neuronal activation, but there are no storage or formal uptake pathways, although NO is rapidly inactivated *in situ*. Under normal physiological conditions, NO has been reported to mediate and/or maintain synaptic plasticity both long-term potentiation (LTP) and long-tern depression (LTD); activated sGC couples neuronal activity to cerebral blood flow and facilitates the release of various

neurotransmitters and hormones (20). NO may also act in concert with other retrograde messengers such arachidonic acid, platelet activating factor (PAF) or carbon monoxide (CO) to regulate synaptic plasticity.(21) The manipulation of central NO levels can markedly affect sympathetic outflow, and hence, systemic blood pressure, alter respiratory rhythm and influence pain thresholds in spinal cord, which suggests that NO is capable of modifying the electrical activity of neurons.(20)

"Nitrergic" is the adjectival term coined to describe the mode of transmission that involves NO and by extension, the transmitter and the nerves from which it originates. (22) There is evidence that the nitrergic transmitter is not NO. It is possible that the nitrergic transmitter is not identical in all tissues and its nature may depend on the local availability of thiols or other compounds that can form NO adducts (such as nitrosothiol). The nitrergic transmitter is formed on demand and a preformed store is sparse or absent. (23) Gastrointestinal smooth muscle function is regulated by nonadrenergic noncholinergic (NANC) nerves which, when stimulated produce relaxation. Several studies support NO as one mediator of NANC transmission.(4) NO protects gastric mucosal lining from gastric contents by increased blood flow (by neural regulation) to allow for adequate perfusion. Thus NO is involved with muscle relaxation, the hemodynamic control and the cytoprotection of gastric lining. (24)

Lot of information is pouring in with regard to NO as NANC neurotransmitter in specific organs and regions including skeletal muscles, pancreatic islet cells, urinary tract, genital system and others wherein it is generated by nNOS isozyme.(4) NO also mediates penile erection by relaxing smooth muscle in the corpus cavernosum.(25)

Conclusion

NO is a tiny free radical and its ubiquitous presence virtually in all tissues suggests its involvement in almost all physiological functions. However, its role in cell damage

and tissue injury makes it a double edged sword. The diverse and important physiological roles of NO suggest that exogenous donation of NO may be useful for the treatment of some disease states. The biology of NO has advanced enormously in the past two decades so that we are clearly now on the thresholds of discoveries that will lead to new clinical strategies in the several areas.

Once considered as toxic environmental pollutant, NO comes of age calling shots. This Cinderella story of NO made the scientific community to rethink over the molecules which are presently being considered ugly.

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