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Nitric Oxide Synthase and Oxidative Stress: Regulation of Nitric Oxide Synthase

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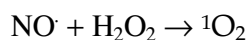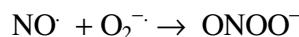*Egypt*

1. Introduction

Nitric oxide has been found to play an important role as a signal molecule in many parts of the organism as well as a cytotocic effector molecule of nonspecific immune response. Nitric oxide is very important functions both in helminthes and mammalian hosts. Nitric oxide may react with proteins and nucleic acids. In addition to binding to heme groups, e.g. of guanylate cyclase, hemoglobin, and cytochrome C oxidase, NO may react with nucleophilic centers like sulfur, nitrogen, oxygen and aromatic carbons. The prime target for covalent binding of NO to a functional groups in proteins under physiological condition in the presence of oxygen are SH groups. The intra-mitochondrial reaction of NO with superoxide anion yields peroxynitrite, which irreversibly modifies susceptible targets within the mitochondria, inducing oxidative and/or nitrative stresses. The signal molecule of NO is synthesized by constitutive nitric oxide synthase (cNOS). The killer molecule NO is synthesized by inducible NOS (iNOS). There is no signal or killer NO – it depends on the environments and partners involved – be very careful in that. Yes, the production is regulated in different ways. Inducible NOS is induced by numerous inflammatory stimuli, including endotoxin, cytokines and excretory/secretory products (ESP) of helminthes. ESP directly interact with the immune system and modulate host immunity. Nitric oxide is a highly reactive and unstable free radical gas that is produced by oxidation of L- arginine by oxygen and NADPH as electron donor to citrulline mediated by a family of homodimer named nitric oxide synthase. In addition to L- arginine-NO pathway, L-arginine is also metabolized to L-ornithine and urea by arginase enzyme. A side from blocking NO synthesis by depleting the cell of substrate for NOS, the arginase-mediated removal of L-arginine inhibits the expression of inducible NOS (iNOS) by repressing the translation as well as the stability of iNOS protein. Furthermore, arginase may inhibit iNOS-mediated NO production through the generation of urea.

2. Chemistry of nitric oxide

Nitrogen monoxide, called nitric oxide (NO) is an endogenous short lived free radical that freely diffuses within cells from formation to action site. Nitric oxide exhibits an enormous

range of important functions in the organism. Nitric oxide interacts with other biomolecules and can combine with superoxide anion (another free radical) to form an unstable intermediate peroxynitrite which may initiate tissue injury. Peroxynitrite may also decompose to form a strong oxidant hydroxyl radical. Nitric oxide, peroxynitrite and hydroxyl radical are capable of oxidizing lipids, proteins, and nucleic acids. Nitric oxide is also a major signaling molecule in neurons and immune system, either acting on the cell in which it is produced or by penetrating cell membranes to affect adjacent cells (Zhang and Li, 2006).

Nitric oxide has been shown to be a mediator of cell injury in some pathological conditions. NO has toxic effects at high concentrations, it reacts with oxygen and superoxide. The product of the reaction with superoxide is peroxynitrite (ONOO-), also it is which decompose to form $\cdot$OH radical. Reaction of nitric oxide and H_2O_2 yields singlet oxygen ($^1O_2$). Also, the reaction pathway of NO with molecular oxygen yields nitrogen diioxide (NO_2) and dinitrogen trioxide (N_2O_3).

$$NO^\cdot + O_2 \rightarrow ONOO^-, NO_2^\cdot, N_2O_3$$

$$NO^\cdot + O_2^{-\cdot} \rightarrow ONOO^-$$

$$NO^\cdot + H_2O_2 \rightarrow {}^1O_2$$

Nitric oxide secreted by activated cells to be a complex "cocktail" of substances. The effect of these reactive species is particularly relevant to cell injury (Rosen *et al.*, 2002).

3. Nitric oxide synthases: Structure and function

Nitric oxide is a highly reactive and unstable free radical gas that is produced by oxidation of L-arginine by oxygen and NADPH as electron donor to citrulline mediated by a family of homodimmer named nitric oxide synthase. In addition to L-arginine-NO pathway, L-arginine is also metabolized to L-ornithine and urea by arginase enzyme (Durante *et al.*, 2007).

The nitric oxide synthase isoforms include the neuronal type I, (nNOS), the inducible form type II (iNOS) and endothelial type III (eNOS), whereas the nNOS and eNOS are constitutively expressed enzymes (cNOS). Constitutive nitric oxide synthase produces NO for short period of time (seconds to minutes). Inducible nitric oxide synthase expression is induced by inflammatory cytokines and toxins leads to the production of much higher amounts of NO compared to the cNOS, once iNOS expressed produces NO for long period of time (hours to days). Inducible NOS typically synthesizes 100-1000 times more than constitutive nitric oxide synthase. The major differences between cNOS and iNOS activities do not reside in the concentrations of NO generated per enzyme, but rather in the duration of NO produced. In addition, iNOS protein content in fully activated cells may be higher than cNOS content. Thus, cytotoxicity usually correlates with the product of iNOS and not with the product of the two cNOS. Thus the regulated pulses versus constant unregulated NO synthesis differentiates between messenger and the killer properties of NOS (Rabelink and Luscher, 2006).

The constitutive form of NOS is anchored on the internal surface of the endothelial cell membranes continuously present, although not always active. Its activity by the endothelial cells and neurons is responsible for maintenance of physiological homeostasis such as blood

pressure and blood flow, controlling leukocyte - endothelial interactions and signaling among neurons. The constitutive isoform was distinguished from the inducible form based on the dependence of the constitutive enzyme activity on calmodulin (Wendy *et al.,* 2001). Other cofactors required for all enzyme forms are flavin mononucleotide, flavin adenine dinucleotide, heme and tetrahydrobiopterin. The constitutive enzyme requires calcium ion (Ca^{2+}) for activity while the inducible enzyme dose not (Wendy *et al.,* 2001).

The inducible NOS form represents a newly synthesized enzyme, which is expressed in response to specific stimuli, such as endotoxin and cytokines leading to enhanced NO production for many hours without further stimulation. It is expressed in multiple cell types, including macrophages, vascular smooth muscle cells, vascular endothelial cells and hepatocytes. The expression of iNOS may be beneficial in host defense or in modulating the immune response; indeed, the massive NO production by iNOS from macrophages during infections inhibits the growth of many pathogens (Wendy *et al.,* 2001; Madar *et al.,* 2005).

Nitric oxide synthase protein is a dimer formed of two identical subunits. There are three distinct domains in each NOS subunit: a reductase domain, a calmodulin-binding domain and an oxygenase domain (Li and Poulos, 2005).

1. **The reductase domain**: This domain contains the flavin adenine dinucleotide (FAD) and flavin mononucleotide (FMN) moieties and acts to transfer electrons from NADPH to the oxygenase domain of the opposite subunit of the dimer, and not to the domain of the same subunit.
2. **Calmodulin-binding domain**: The binding of calmodulin is required for the activity of all the NOS isoforms. It connects NO and calcium homeostasis.
3. **The oxygenase domain**: This domain contains the binding sites for tetrahydrobiopterin, heme and arginine. The oxygenase domain catalyzes the conversion of arginine into citrulline and NO.

Several factors affect the synthesis and catalytic activity of iNOS particularly, dimerization of NOS monomers. NOS isoforms are only active as homodimers. The dimerization of NOS monomers is promoted by heme, resulting in rapid conformational changes that, by cooperative action of tetrahydrobiopetrin (BH4) and L-arginine, leads to a stable and active enzyme. Moreover, an intracellular depletion of heme, BH4 and/or L-arginine considerably contributes to decreased resistance of NOS enzymes to proteolysis (Dunbar *et al.,* 2004).

4. Molecular nitric oxide targets in cells

The broad spectrum of effects performed by NO can be exerted through two main mechanisms: the activation of guanylate cyclase (which can be soluble in the cytosol or coupled to the cell membrane) or through its interaction with the major cellular source of superoxide anion, the NO/cytochrome C oxidase, which is found in mitochondria (Ghafourifar and Cadenas 2005; Poulos 2006).

The guanylate cyclase-dependent effects of NO mainly affect the vascular tonus thereby affecting the inflammatory reaction by increasing synthesis of guanosine 3',5'-monophosphate (cGMP), it acts as inhibitors of platelets aggregation. Other effects pertaining to mitochondrial functions involve the respiratory burst. Mitochondria can produce NO through its own Ca^{2+}-sensitive synthase (mitochondrial, mtNOS). This enzyme

regulates mitochondrial oxygen consumption and transmembrane potential via a reversible reaction with cytochrome C oxidase. The intramitochondrial reaction of NO with superoxide anion yields peroxynitrite, which irreversibly modifies susceptible targets within the mitochondria, inducing oxidative and/or nitrative stress (Ghafourifar and Cadenas 2005).

In addition to their primary role in the production of energy (ATP), mitochondria generate reactive oxygen species (ROS) that can directly or indirectly affect the NO response. Since NO and ONOO⁻ can inhibit cellular respiration at the level of cytochrome C oxidase and complexes I-III, respectively, it has been suggested that mitochondrial function can influence the balance between apoptosis and necrosis induced by NO. Nitric oxide can stimulate the biogenesis of mitochondria in a guanosine 3',5'-monophosphate (cGMP)-dependent manner (Nisoli *et al.* 2003; Poderoso 2009).

Nitric oxide may react with proteins and nucleic acids. In addition to binding to heme groups, e.g. of guanylate cyclase, hemoglobin, and cytochrome C oxidase, NO may react with nucleophilic center like sulfur, nitrogen, oxygen and aromatic carbons. The prime target for covalent binding of NO to a functional groups in proteins under physiological condition in the presence of oxygen is the SH group. NO has been shown to N-nitrosylate primary arylamine of nucleotides and subsequent hydrolysis yield deamianted nucleotide. NO also mediates Fe^{+2} release from target cells, destroying Fe-S clusters in enzymes, like the citric acid cycle enzyme aconitase or ferrocheletase, which catalyse Fe^{+2} into protoporphyrin. NO can inhibit several interacellular enzymes and profoundly affect the cellular gene transcription machinery (Laurent *et al.,* 1996; Alderton *et al.,* 2001).

The high toxicity of inducible NO comes from its high concentration and from its reactivity with oxygen and oxygen-related reactive intermediates, which yield numerous toxic species that have enzymatic and DNA-damaging properties (Alderton *et al.,* 2001).

Depletion of glutathione, inhibition of mitochondrial superoxide dismutase (SOD), and perhaps the loss of other antioxidant defense mechanisms could permit a rise in the endogenous level of reactive oxygen species normally produced by metabolism, which is likely to enhance the toxicity of NO. By this route, reactive nitrogen and oxygen species may act in concert to inactivate the key metabolic enzymes and cause lipid peroxidation and DNA strand breaks that result in irreversible cell injury and death (Radi, 2004; (Hummel *et al.,* 2006).

5. Protective and cytotoxic function of nitric oxide

In the cardiovascular system, nitric oxide plays a major role in the regulation of blood flow and blood pressure as well as the general homeostatic control of the vasculature. Nitric oxide also inhibits platelet aggregation and adhesion by a mechanism dependent on cyclic GMP. It may also be involved in the interaction of leucocytes with vessel walls, since it inhibits leukocytes activation (Bian *et al.,* 2008).

NO reacts with iron in the active side of the enzyme guanylate cyclase (GC), stimulating it to produce the intracellular mediator cyclic (cGMP), that in turn enhances the release of neurotransmitters resulting in smooth muscle relaxation and vasodilation (Esplugues, 2002).

In the central nervous system, accumulating evidence indicates that nitric oxide plays a part in the formation of memory. It is also found in some peripheral nerves, where it may contribute to sensory transmission (Sunico *et al.,* 2005; Zochodne and Levy, 2005).

The effects of NO can be direct or indirect and can influence several physiological processes, ranging from DNA transcription and replication to protein synthesis and secretion. Under physiological conditions, NO mediates homeostatic anti-inflammatory reactions, such as inhibition of neutrophil adhesion, cyclooxygenase activity, cytokine production, osteoclast bone resorption, among others, in order to prevent autoimmunity (Dal -Secco *et al.,* 2006; Fukada *et al.,* 2008; Livonesi *et al.,* 2009).

Generation of NO by endothelial cells causes smooth muscle relaxation through activation of guanylate cyclase by nitrosation of its heme group. It is hypothesised that NO may have originated in host as a mechanism of first-line defense against intracellular pathogens. This theory has been confirmed by the wide occurrence of the enzyme responsible for NO production, NO-synthase, in several species, ranging from invertebrates to mammals and non-mammalian vertebrates (Ribeiro *et al.,* 1993; Fukada *et al.,* 2008).

In mammals, NO production is upregulated in response to infection by a wide range of unicellular organisms such as bacteria, yeast and parasites (Cardoni *et al.,* 1990). Evidently, evolutionary diversity has induced NO synthesis to be performed in response to different kinds of stress stimuli. In fact, several antigens derived from intracellular parasites can be recognized by innate immune receptors on macrophages, triggering NOS activity (MacMicking *et al.,* 1997; Livonesi *et al.,* 2009).

Nitric oxide plays a significant role in acute and chronic inflammation i.e. excessive production of NO contributes to vasodilation and tissue damage which characterize many inflammatory conditions. Also, NO appears to play an important role in the functions of immune system as a cytotoxic macrophage effector molecule, modulator of polymorphonuclear leucocytes chemotaxis and adhesion, mediator of tissue injury caused by adhesion of immune complexes, and a regulator of lymphocyte proliferation (Shah *et al.,* 2004).

Cytokines and NO can modulate the production of chemokines and adhesion molecules in vivo and in vitro, influencing the course of infection (Savino *et al.,* 2007; Machado *et al.,* 2008). Chemokine receptors are also involved in cellular activation during parasitic infections and this G-protein-coupled signalling pathway is implicated in NO production as well (Benevides *et al.,* 2008).

NO is perhaps the most important among the group of early mediators produced by cells of the innate immune system. Phagocytes constitute the first line of microbial defense and they function by sensing the presence of different types of infectious agents (Carneiro-Sampaio and Coutinho, 2007) through pattern recognition receptors, including Toll-like receptors (TLRs) and the most recently described NOD- (NLRs) receptors. These receptors recognize multiple microbial patterns; therefore, they are critical for triggering the production of inflammatory mediators and essential for activation of the adaptive immune response (Schnare *et al.,* 2001; Kanneganti *et al.,* 2007; Underhill, 2007).

Nitric oxide synthase is produced by antigen-presenting cells (APC) during antigen processing and presentation to T cells and it can modulate various functions of APCs. It can inhibit the expression of major histocompatibility complex class II molecules in activated

macrophages and, at high concentrations, may also inhibit IL-12 synthesis, thus contributing to the desensitization of macrophages after exposure to inflammatory stimuli (Salvucci *et al.,* 1998; Pahan *et al.,* 2001; van der Veen, 2001). In chronic immune responses to intracellular pathogens, NO is reported to play a regulatory role and may promote parasite persistence. For these reasons, it is suggested that NO is cytostatic rather than cytotoxic for parasites (Jana *et al.,* 2009).

NOS enzymes or NO-activity-derived products (nitrites or nitrotyrosine) have been detected in different locations of adult worms. Neural NOS and iNOS have been found in the nervous tissue and in the parenchyma of *Schistosoma mansoni* respectively (Kohn *et al.,* 2001). The presence of NOS has been also demonstrated in *Ascaris suum*; *Toxocara canis*; *F. gigentica* (Fan *et al.,* 2004; Hamdi and Ali, 2009). Nitric oxide synthase is located in the muscular wall from adult worms in *Brugia malayi*, *Dirofilaria immitis* and *Acanthocheilonema vitae* filariae (Pfarr *et al.,* 2001). Expression of endothelial NOS (eNOS) has been detected in the cuticle and stichocytes from *Trichinella britovi* (Masetti *et al.,* 2004). Nitrites have been detected in the hydatid liquid of fertile *Echinococcus granulosus*. Expression of iNOS and nNOS has been detected in the parenchyma and nervous structures of the filariform larvae from *Strongyloides venezuelenesis*. Moreover, NOS expression has also been demonstrated in other phases, such as eggs, sporocysts, and cercariae of *Schistosoma* sp. (Long *et al.,* 2004) and other structures as oocytes, spermatozoids, and embryonic forms of *Brugia malayi* (Pfarr *et al.,* man 2001).

A dual role in the immunity is usually observed for NO. This well-known immune duality is usually dependent on concentration and, once dysregulated, may lead to host cell toxicity, autoimmunity or parasite persistence due to immune evasion, all of which can lead to pathology. The strength of NO toxicity is dependent on the sensitivity of the parasite, which differs among parasite strains and according to the physiological microenvironment (Gutierrez *et al.,* 2009).

Specifically, both adult worms' excretory/secretory antigens and larval somatic antigens of *T. canis* are capable of stimulating *in vitro* the production of NO at transcriptional level in rat alveolar macrophages. The stimulation of NO production by antigens of *T. canis* LII (extracted from excretory/secretory product) does not seem to play a host-defensive role. The production of NO by host cells, activated by the parasite, has negative effects not on parasite survival but on the host, and thus putatively represents a parasite evasion mechanism. Types of parasite evasion/adaptation mechanisms largely depend on the parasite's migration and definitive anatomical location. *T. canis* is characterized by its dissemination (migration) through the bloodstream until it reaches its final inside the host. This bloodstream migration would be clearly facilitated by blood-vessel dilatation described toxocariasis models. Deleterious effects were attributed on the host physiology in the release of NO by host cells, induced by the parasite itself (Espinoza *et al.,* 2002). Thus, production of NO during migration of *T. canis* LII inside their host could facilitate their migration and triggering of this production by LII may represent a parasite adaptation mechanism (Muro and Perez-Arellano, 2010).

The effect of different antigens of excretory/secretory of larval and adult worms of nematodes, on NO production from rat alveolar macrophages was observed. Excretory/secretory antigens from adult worms in *Toxocara canis* and *Strongyloides venezuelensis* stimulated the NO production from alveolar macrophages (Espinoza *et al.,*

2002). The cytoplasmatic signalling pathways involved in the NO production after stimulation with adult excretory/secretory antigen of *Toxocara canis*. It was suggested that phospholipase C macrophage pathways play an essential role in activating the production of NO triggered by this antigen. This suggests that NO production could be due to an increase of intracellular calcium and activation of the arachidonic acid pathway. Moreover, *Toxocara canis* excretory/secretory adult antigen also stimulated alveolar macrophages to produce prostaglandin E_2 (PGE_2). These results indicate that *Toxocara canis* can stimulate the release of vasodilatory mediators by host macrophages (Espinoza *et al.*, 2002; Hewitson *et.al*, 2009; Muro and Perez-Arellano, 2010).

6. Regulation of nitric oxide synthase

Inhibition of arginase has been shown to stimulate NO synthesis in endothelial cells. In addition, overexpression of arginase I or arginase Π supresses NO generation in endothelial cells and this is associated with a significant decrease in intracellular L- arginine content (Li *et al.,* 2001). Interestingly, constitutive expression of arginase in microvascular endothelial cells counteracts NO-mediated dilation, suggesting that arginase subserves a tonic vasoconstrictor function (Chicoine *et al.,* 2004; Johnson *et al.,* 2005).

A side from blocking NO synthesis by depleting the cell of substrate for NOS, the arginase-mediated removal of L- arginine inhibits the expression of inducible NOS (iNOS) by repressing the translation as well as the stability of iNOS protein. Furthermore, arginase may inhibit iNOS-mediated NO production through the generation of urea. These findings suggest that arginase downregulates NO formation via multiple mechanisms. Interestingly, N-hydroxy-L-arginine, an intermediate formed during the catalysis of L-arginine by NOS, is a potent inhibitor of arginase, suggesting that NOS may also influence arginase activity (Johnson *et al.*, 2005).

Thus, arginase has recently been emerged as a critical regulator of NO synthesis that may contribute to the development of numerous pathologies, including vascular disease. The release of NO by endothelial NOS (eNOS) plays a crucial role in preserving vascular homeostasis. In response to changes in shear stress or receptor stimulation, NO is released from the vascular endothelium to promote blood flow by inhibiting vascular tone and platelet aggregation (Durante, 2007).

Aminoguanidine has effects on several enzyme systems. It interferes with non-enzymatic glycosylation. Aminoguanidine inhibits nitric oxide synthase (NOS), particularly its inducible form (iNOS), reducing the pathological effects due to over-activity of these enzymes and thus to over-production of NO. Aminoguanidine may affect of polyamine metabolism (Kolodziej *et al.*, 2006).

NO synthesis inhibitors have been used in vivo to evaluate their effect on parasitic infection. This strategy has mainly been used in experimental models of filariosis by *Brugia malayi*, toxocariosis, *trichinellosis*, and strongyloidiasis. The results obtained are divergent, since the use of aminoguanidin diminishes the lesions in toxocariosis, whereas it increases the parasite load in filariosis and strongyloidiasis. Moreover, mice treated with aminoguanidine, at the beginning of muscle phase of the infection, inhibit the reduction of muscle larvae number and cells of inflammatory infiltrates did not show any specific iNOS

reaction]. Influence of the inhibition of the NO production by iNOS in a toxocariosis experimental model decreases the deleterious effects of the parasite upon the host, especially the lung vascular alterations (Muro and Perez-Arellano, 2010).

Oxalomalate, a tricarboxylic acid structurally related to citrate, has long been known to be a powerful competitive inhibitor of both aconitase, which is required for the first step of citric acid cycle, and NADP dependent isocitrate dehydrogenase. NO modulates also the activity of several other proteins including mitochondrial aconitase, an iron-dependent enzyme and isocitrate dehydrogenase (Irace *et al.*, 2007).

OMA inhibits aconitase and isocitrate dehydrogenase, the Krebs cycle flux appears to be constricted at two steps with a consequent reduction of its biosynthetic ability caused by the limited availability of the successive intermediates, namely α-ketoglutarate, a precursor of L-arginine, and succinyl-CoA, a precursor of heme. In fact, exogenous treatment with α-ketoglutarate or succinyl-CoA partially or almost completely restored NO production which was inhibited by OMA. As heme is the sole cofactor absolutely required for the formation of active NOS dimers and the binding of L-arginine to iNOS facilitates its dimerization, the partial slowdown of Krebs cycle induced by OMA, leading a consequent decrease of succinyl-CoA and α-ketoglutarate formation, could explain the effect of OMA on NO production. Moreover, inhibition by OMA of the $NADP^+$-dependent isocitrate dehydrogenase reduces the availability of NADPH, a source of electrons in the NOS enzymatic reaction.This impairment, together to the depletion of L-arginine caused by α-ketoglutarate shortage, may prevent NO biosynthesis(Irace *et al.*, 2007).

It is known that NOS are long-lived proteins and the presence of heme and L-arginine or BH4 considerably contributes to their resistance to proteolysis. Consequently, the coupled shortage of heme and L-arginine caused by OMA may determine instability of NOS dimers, and consequently, lower resistance to proteolysis. This hypothesis is supported by the observed reduction of iNOS protein content both in LPS-stimulated macrophage treated with OMA and in peritoneal macrophages recovered from LPS-stimulated rats after injection of OMA precursors (Osawa *et al.*, 2003).

7. Conclusion

It is well known that, glutathione interacts with reactive species derived from NO oxidation and converts these species to less toxic ones Therefore, depletion of glutathione, inhibition of mitochondrial superoxide dismutase (SOD), and perhaps the loss of other antioxidant defense mechanisms could permit a rise in the endogenous level of reactive oxygen species normally produced by metabolism, which is likely to enhance the toxicity of NO development of NOS inhibitors constitutes a current strategy in the research of new compounds showing interesting properties. Inhibition of NO production would be beneficial for the host

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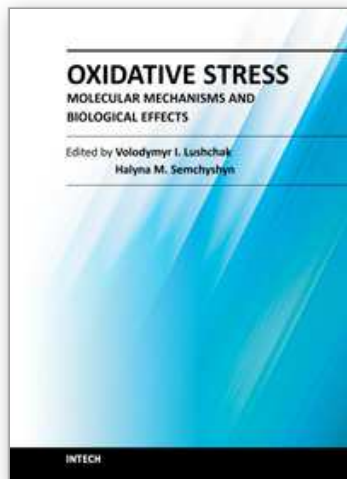
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Edited by Dr. Volodymyr Lushchak

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