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L-Arginine-Nitric Oxide Pathway: Its Relevance in Human Biological Processes

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Abstract

Human cells generate nitric oxide (NO) using molecular oxygen and nitrogen provided by l-arginine through a reaction catalyzed by specific oxido-reductases (nitric oxide synthases) of which three isoforms exist. Numerous pathways are known to be available for l-arginine synthesis nitric oxide is a vital bioactive molecule implicated in the regulation of cardiovascular, immune, and nervous systems. Its deficiency gives rise to many human pathological states, thus presenting biological basis for the utilization of nitric oxide replacement therapy to supplement nitric oxide for normal biological functions. Likewise, production of excess NO can lead to pathological states such as oxidative stress, lung injury, acute and chronic inflammatory processes, stroke and other neurodegenerative diseases. As an antithrombotic agent, NO exerts important antiadhesive, antiplatelet, antiproliferative, antioxidant and vasodilatory effects. The objective of the review study is to provide comprehensive information on L-arginine-nitric oxide pathway that will be of great assistance to scientists interested in nitric oxide (a physiological intriguing chemical substance) properties.

Keywords: *L-Arginine; Nitric Oxide; Roles and Therapeutic Utilization of Nitric Oxide*

Introduction

The regulation of l-arginine-nitric oxide pathway happens at the level of nitric oxide generation [1,2]. Nitric oxide (NO) a potentially toxic gas with free radical properties is synthesized from l-arginine by the catalysis of a physiological enzyme termed nitric oxide synthase (NOS) [3,4].

As a potent vasodilator, it activates soluble guanylate cyclase (sGC) in vascular smooth muscle cells to catalyze the conversion of guanosine triphosphate (GTP) to cyclic guanosine monophosphate (cGMP). In the absence of receptors, nitric oxide has the ability to regulate normal physiological activities and also mediate cytotoxicity events under pathological conditions. For instance, it has been implicated in the pathophysiology of metabolic syndrome characterized by abdominal adiposity, dyslipidaemia, elevated blood pressure, glucose intolerance, and insulin resistance [5].

Nitric oxide has mediated the effects of excitatory amino acids in the central nervous system (CNS). As an endogenous stimulator in the tissues within the CNS, its pathway acts as a transduction mechanism for the soluble guanylate cyclase. It has also been implicated in either the induction or protection against oxidative stress within various tissues [6]. Oxidative stress causes damage on biomolecules such as lipids, proteins and nucleic acids in tissues.

In addition to l-arginine-nitric oxide pathway, other sources (endogenous or exogenous) of nitric oxide in human body include:

1. Endogenous sources:

(i) Platelets- produce NO, which modulates their aggregability.

(ii) Immunological stimulation- stimulation in macrophages, neutrophils, and other cells release NO. The NO thus released acts as part of the host defense mechanism.

(iii) Vascular endothelial cells- account for the biological properties of nitric oxide (endothelium-derived relaxing factor). The NO produced by endothelial cells rapidly diffuses to adjacent vascular smooth muscle cells to raise cGMP thereby decreasing cytosolic calcium followed by inhibition of the calcium-calmodulin myosin light chain kinase-complex formation, and resulting in vasorelaxation.

(iv) *In vivo* recycling of inorganic anions nitrate (NO_3^-) and nitrite (NO_2^-)- produces nitric oxide. This involves bioactivation (conversion) of nitrate by commensal bacteria inhabiting the gastrointestinal tract to nitrite through reduction process. The nitrite formed is reduced to nitric oxide in blood and tissues by a multitude of enzymatic and nonenzymatic mechanisms [7]. These nitrite reduction pathways in the body utilize ascorbate, haemoglobin, myoglobin, xanthine oxidoreductase, polyphenols and protons.

(v) Vegetables namely beetroot, lettuce, spinach are vital sources of dietary nitrates and have the ability to produce nitric oxide *in vivo* through the nitrate-nitrite-nitric oxide pathway [8].

(vi) Hypoxia and acidosis (acidic condition)- employ the nitrate-nitrite-nitric oxide pathway. This pathway (a backup system when NO output from NOS is low ensures NO bioactivity) has been suggested to contribute to physiological cellular response to ischaemic stress, hypoxic signaling, modulation of cellular respiration and vasodilation by releasing nitric oxide from storage form of nitric oxide (nitrite) catalyzed by a number of nitrite reductases.

2. Exogenous sources:

(i) Cigarette smoke- is a particularly rich source of NO and nitrogen dioxide [9].

(ii) Therapeutic agents- provide NO while eliciting their biological effects on certain human diseases such as gastric ulceration, myocardial infarction, pulmonary and systemic hypertension, and stroke etc. Such therapeutic agents include antihypertensive agents and hybrid nitric oxide donors, diazeniumdiolates, S-nitrosothiols, organic nitrates, sodium nitroprusside, and sydnonimines etc.

Discussion

Nitric oxide synthase (NOS) isoforms

Three isoforms of NOS exist namely neuronal NOS (nNOS), inducible NOS (iNOS), and endothelial NOS (eNOS) [10]. The nNOS and eNOS isoforms, are expressed to a greater extent in neuronal and endothelial cells, respectively, while the iNOS isoform is expressed in many nonvascular cell types such as fibroblasts, hepatocytes, macrophages, and endothelial cells [11]. Furthermore, functionally iNOS produces NO in response to inflammatory mediators, whereas nNOS and eNOS generate NO as a signaling molecule to regulate physiologic processes such as vasodilatation [12]. In addition, NO biosynthesis through iNOS is a calcium-independent process, but the biosynthesis of NO through nNOS and eNOS is a calcium- and calmodulin (CaM)-dependent process [13].

L-arginine synthesis

L-arginine is a substrate required for the synthesis of nitric oxide by nitric oxide synthase. Absorbed glutamine is converted to citrulline and ammonia in gastrointestinal tract. As both enter the liver, ammonia is metabolized to urea, while citrulline enters into systemic

circulation and get metabolized to arginine and urea in the kidney [14]. This pathway produces approximately 60% of arginine whereas endothelium cell pathway generates about 15% of arginine [15,16]. As a substrate for urea synthesis in the kidney, arginine conversion to citrulline and urea in the kidney is catalyzed by the enzyme arginase [17]. Furthermore, arginine can be synthesized from citrulline following citrulline's conversion to argininosuccinate by argininosuccinate synthase and conversion from argininosuccinate to arginine by argininosuccinate lyase [18].

Physiological roles or functions of l-arginine-nitric oxide pathway in many diverse processes

The pathway has generated potential novel therapies for- (i) bronchodilation, (ii) platelet aggregation, (iii) leukocyte adhesion to the endothelium, (iv) damage caused by an ischemia/reperfusion insult [19]. The pathway has also played very vital physiological functions in many diverse processes namely (a) neurotransmission (as a neurotransmitter in glutamatergic nerves in the central and peripheral nervous systems), (b) normal functioning of the genitourinary system, (c) regulation of blood flow (vasodilatation of blood vessels and lowering of blood pressure), (d) immune responses, (inflammation response and host defense; microbicidal mechanisms of macrophages), (e) myocardial contractility, and thrombosis [20-23].

Potential disease states associated with l-arginine-nitric oxide pathway

(i) Oxidative stress- nitric oxide as a modulator of cellular function can exert effect either as a cellular messenger or, when produced in excess quantities, as pro-oxidant, inducing oxidative stress [24,25].

(ii) Lung injury- under normal conditions, interaction of nitric oxide with superoxide anion protects lungs against superoxide, however production of excess NO and superoxide leads to very rapid reaction of both compounds to generate a very powerful oxidant (peroxynitrite), that has the capacity to injury the lung [26]. Typical examples of such diseases arising from lung injuries are (a) asthma (b) chronic inflammatory disorder of the airways involving airway epithelium, eosinophils, mast cells, neutrophils, T-lymphocytes etc [27].

However, nitric oxide as a bronchodilator, may be beneficial in asthmatic patients if high concentration is inhaled by counteracting the bronchoconstriction produced by inflammatory mediators such as leukotriene D4 [28,29].

(iii) Arterial hypertension- insufficiency of nitric oxide due to endothelial dysfunction has been implicated with arterial hypertension [30]. Arterial hypertension is characterized with increased vascular tone of resistance vessels, reduced compliance of conduit arteries, and thickening of the intima-media [31].

(iv) Hypotension accompanying septic shock- enhanced adverse effect that occurs if soluble guanylate cyclase (sGC) stimulators (example riociguat) is combined with phosphodiesterase 5 (PDE5) inhibitors (examples sildenafil and tadalafil) [32,33].

(v) Atherosclerosis- due to impaired NO-sGC-cGMP signaling which triggers endothelial dysfunction [34]

(vi) Neurotoxic effects such as stroke and other neurodegenerative disorders due to increased formation of nitric oxide [23].

(vii) Acute and chronic inflammatory processes due to overwhelming production of nitric oxide [35].

Nitric oxide synthase inhibitors

The implication of nitric oxide in various pathological processes, has prompted the view that nitric oxide synthase is as important pharmacological target, hence the development and utilization of specific NOS inhibitors. The potential or clinical inhibitors include:

(i) N-methyl-L-arginine (L-NMA)- is a degraded product of arginine-methylated proteins and occurs naturally in living organisms. Widely used to decrease nitric oxide bioavailability or establish the nitric oxide dependency of a physiological process [36,37]. It acts as a competitive inhibitor of all the isoforms of nitric oxide synthase [38].

(ii) N-nitro-L-arginine (L-NNA)- is one of the first synthetic NOS inhibitors. It is reported to be a competitive inhibitor of all isoforms of the enzyme, however, with high selectivity to two isoforms [39].

(iii) L-N-nitroarginine methyl ester (L-NAME)- it acts as a weak NOS inhibitor. It is a prodrug of N -nitro-L-arginine that is readily hydrolyzed by ubiquitously esterases to N -nitro-L-arginine in a biological system [40].

(iv) L-N, N-dimethylarginine (ADMA)-is an asymmetrically compound, and a naturally occurring inhibitor of NOS. ADMA is a product of the degradation of arginine-methylated proteins [41]. It is a nonspecific competitive inhibitor of the enzyme isoforms but has been suggested to be a potent inhibitor of one of the isoforms (nNOS) [42].

(v) L-N-amino-L-arginine- is a synthetic nonselective competitive inhibitor of enzyme isoforms [43]. Extensively used to block NO release from endothelial cells and aortic rings [44].

(vi) L-N-propylarginine (L-NPLA)- is one of synthetic alkylated arginines that inhibits NOS reversibly with a strong preference for nNOS and currently undergoing clinical trials [45].

(vii) N-(1-iminoethyl)-L-lysine 5-tetrazole-amide (LNIL-TA)- is a prodrug of N-(1-iminoethyl)-L-ornithine (L-NIO), which is a potent nonselective competitive inhibitor of nitric oxide synthase. It is used orally in the treatment of asthma [46]. N-(1-iminoethyl)-L-ornithine is the only natural amidino amino acids derivatives.

(viii) (2S)-2-amino-4-{[2-(ethanimidoylamino)ethyl]thio}butanoic acid (GW274150)- is an amino acid sulphide that has exhibited the most potent and selective inhibitory action to recombinant human iNOS.

It has undergone clinically trials for the treatment of asthma and rheumatoid arthritis [47,48].

Other synthetic derivatives that have exhibited competitive inhibitory properties on NOS isoforms are: N(ω)-allyl-L-arginine [49]; NG-cyclopropyl-L-arginine [50]; N-(1-imino-3-butenyl)-Lornithine (vinyl L-NIO, L-VNIO); N-[2-(methylthio)-1-iminoethyl]-L-ornithine; and N-(1-iminoethyl)-L-lysine (L-NIL) [51,52].

Therapeutic agents that release nitric oxide or enhance its bioactivity for the potential treatment of human diseases:

These therapeutic agents include nitric oxide donors (directly or indirectly release nitric oxide) and agents that increase nitric oxide bioactivity. They include:

(A) Direct nitric oxide donors [53-55]: These spontaneously release nitric oxide, and do not require metabolism and bio-transformation. Typical examples are:

(i) Inhalable clinical nitric oxide gas- clinically utilized for the treatment of multiple respiratory and other cardioresiratory disorders for example, treatment of newborn babies with respiratory distress syndrome, pulmonary hypertension or hypoxic respiratory failure. The inhaled gas acts by dilating only vessels supplying well-ventilated parts of the lungs, resulting in ventilation-perfusion matching increase. Also being selective to the lung, systemic vasodilatation is significantly reduced due to the rapid scavenging of NO in blood.

(ii) Diazeniumdiolates- are complexes formed between a nucleophile and nitric oxide. They act by inhibiting 5-hydroxytrytamine.

Diazeniumdiolates do not require metabolism or redox activation to release nitric oxide at physiologic pH. They are effective in the treatment of pulmonary hypertension. Typical examples are diethylamine/NO, V-PYRRO/ NO and Spermine/NO.

(iii) Sydnonimines- spontaneously release nitric oxide and induce vasodilation through the guanylyl cyclase-3′,5′-cyclic guanosine monophosphate pathway. Typical examples are linsidomine and molsidomine.

(iv) S-nitrosothiols- endogenous, naturally occurring moieties that form when nitric oxide reacts with cysteine thiol in the presence of an electron acceptor to form an S-NO bond. They act as reservoirs of nitric oxide, and upon breakdown by enzyme systems spontaneously release nitric oxide. Typical examples are S-nitrosoglutathione, S-nitroso-N-acetylcysteine, and S-nitroso acetylpenicillamine.

(B) Indirect nitric oxide donors [56-58]: These chemical active compounds require biotransformation, metabolic activity, and reduction-oxidation activation. They include:

(i) Organic nitrates- induce arterial and venous vasodilation in coronary and systemic blood vessels. They act by activating guanylyl cyclase as well as inhibiting calcium channels in vascular smooth muscle cells. Organic nitrates are effective in the treatment of angina pectoris, hypertension and heart failure. Typical examples are amyl nitrite, isosorbide 5-mononitrate, isosorbide dinitrate, and nitroglycerin.

Isosorbide mononitrate is a clinical long-term nitric oxide-releasing drug for hypertension [56]. Nitroglycerin and sodium nitroprusside, are clinical short-acting anti-angina agents to rapidly decrease blood pressure by reducing cardiac preload and afterload and dilating coronary vessels through the release of nitric oxide and formation of cGMP [57,58]. Sodium nitroprusside has primarily been utilized to treat hypertensive crisis and also eases off heart failure symptoms. Toxicity has caused its drawback because it raises levels of cyanide in the body.

Organic nitrates have also been found to play a role in the inhibition of excessive bone resorption, (major mechanism of osteoporosis), promote bone formation, reduce blood pressure, vascular impedance in women with preeclampsia.

(ii) Nicorandil (newer nitrate)- is a nicotinamide ester with a nitrate-like moiety that combines release of nitric oxide with activation of adenosine triphosphate-sensitive potassium channel. It has antianginal effects, coronary and peripheral vasodilatation with reduction in both preload and afterload.

(C) Hybrid nitric oxide donors [59]- synthesized through an ester linkage of nitric oxide-releasing moiety with conventional active agents. Typical examples are non-steroidal anti-inflammatory drugs (NSAIDs) such as NO-aspirin (treatment of vascular disorders and cancer), NO-ibuprofen, NO- flurbiprofen (potential treatment of Alzheimer's disease), NO-diclofenac, NO-nitrofenac, and NO-naproxen. They are very effective in the treatment of inflammatory conditions. Gastrointestinal toxicity has been greatly reduced, in comparison with conventional NSAIDs. Other hybrid NO- drugs are NO- paracetamol (for liver disease), NO- mesalamine and NO-prednisolone (enhance the tolerability of the parent drugs), sildenafil (treatment of impotence), and salbutamol nitrate (treatment of bronchodilation).

(D) Antihypertensive agents [60,61]- some antihypertensive agents tend to directly enhance nitric oxide bioactivity by increasing endogenous production of nitric oxide synthase and release of nitric oxide; preventing the oxidative processes that leads to the degradation and impairment of nitric oxide, promoting expression of the nitric oxide substrate (L-arginine) or nitric oxide cofactors (tetrahydrobiopterin).

Examples are:

(i) Angiotensin-converting enzyme (ACE) inhibitors- enhance nitric oxide release and bioactivity through a number of mechanisms namely: (a) stimulation of bradykinin β receptors, leading to release nitric oxide and other vasoactive substances, (b) protection of nitric oxide against oxidative damage and impairment by suppressing angiotensin II generation, (c) significant improvement in endothelium-dependent vasodilatation in endothelium dysfunction and hypertensive patients. Typical examples are ramipril and quinapril.

(ii) Angiotensin II receptor blockers- enhance nitric oxide bioactivity by (a) providing antioxidant protection against nitric oxide impairment, in contrast to angiotensin-converting enzyme inhibitors, (b) not increasing bradykinin levels in order to release nitric oxide, (c) promoting endothelium function in atherosclerosis and congestive heart disease patients. Typical examples are losartan and candesartan.

(iii) Calcium channel blockers-enhance nitric oxide bioactivity mostly through (a) antioxidant actions in endothelium cells, (b) induce nitric oxide synthase activity by increasing calcium ion concentrations in endothelium cells, (c) improve endothelium-dependent vasodilatation in constricted coronary artery segment, as well as endothelium function in hypertensive patients. Typical examples are amlodipine and nisoldipine.

(iv) Vasodilating β-blockers- promote nitric oxide bioactivity by (a) inducing endothelium-dependent vasodilation mediated through the [-arginine/NO pathway, (b) ameliorating arterial stiffness (a key factor in systolic hypertension). Typical examples are nebivolol and celiprolol.

(v) Statins- promote nitric oxide bioactivity by significantly (a) improving endothelium-dependent vasodilatation in coronary or brachial arteries, (b) decreasing oxidative stress linked with low density lipid cholesterol (LDL-C) reduction (c) reducing vascular prothrombotic and inflammatory factors. Typical example is atorvastatin.

In general, l-arginine-nitric oxide pathway is one of the most important endogenous pathways to generate physiological nitric oxide.

Conclusion

The biosynthesis of nitric oxide (a potent vasodilator) involves the entry of arginine into the nitric oxide synthase pathway and the conversion of arginine to nitric oxide and citrulline. Numerous pathways provide for l-arginine synthesis. A number of cells in the circulation namely endothelial cells (largest source), platelets, red blood cells and white blood cells release nitric oxide. The NO-sGC-cGMP signaling pathway has a number of effects on endothelial cell permeability, gene expression, platelet aggregation, and vascular tone, As an antithrombotic agent, nitric oxide exerts important antiadhesive, antiplatelet (inhibition of platelet adhesion and aggregation), antiproliferative (prevention of smooth muscle cell proliferation), antioxidant and vasodilatory effects. Several pharmacologic strategies (using nitric oxide donors and agents that increase nitric oxide bioactivity) to target the nitric oxide pathway have been developed due to the essential role of nitric oxide in diverse physiologic processes and diseases.

Finally, modulation of the l-arginine-nitric oxide pathway is one of the mechanisms several therapeutic agents namely anti-inflammatory, cardiovascular, sexual dysfunction drugs elicit their biological activities.

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