Role of L-arginine in the biological effects of blue light

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Arginine, a semi-essential amino acid, and metabolites of arginine exert multiple biological effects. It has been known that arginine causes the release of various hormones such as insulin, glucagon, growth hormone, prolactin, and adrenal catecholamines. Arginine infusion also produces vasodilation, and in the kidney increased plasma flow accompanied by increases in glomerular filtration rate (GFR).
Recent studies have showed that blue and red light irradiation in vitro and in vivo can increase production of nitric oxide (NO), superoxide anion, and related reactive oxygen species (ROS). These then can modulate the production and secretion of several cytokines and other mediators and play an important role as regulatory mediators in signaling processes which can then modulate the production, mobilization and homing of stem cells.
It is proposed that some of the therapeutic effects of light can be considered to be due to the changes in the metabolism of L-arginine. The regulation of L-arginine turnover by the use of light at blue wavelengths between 400 nm and 510 nm can be the explanation for some of the observed effects of blue light: lowering of blood pressure, pain killing effect, regulating insulin production, anti-inflammatory action, and possible effects on the release and homing of stem cells.

Introduction

Over thousands of years people know about abilities of sun light to support health. Recent progress in medicine and thechnology introduced UV and laser therapy methods. Several studies and clinical observations during last decades proved the paositive effects of light for the treatment of different pathoplogues. At the same time treatment mecahanisms of lighjt therapy are still on the level of hypotheses. Currently the majority of phototherapy equipment irradiates red and infrared (IR) light, and accordingly the vast majority of doctors and practitioners are using red and IR light for therapy. At the same time data available that treatment effects of the blue region are stronger than in red and IR band. Those observations are made on both – cellular and organism levels.
Arginine, NO-synthase and number of other enzymes can absorb light in the blue region. It is proposed that the regulation of L-arginine turnover by the use of light at blue wavelengths between 400 and 510 nm can be the explanation for some of the observed effects of blue light.

Arginine

Arginine is a semi-essential amino acid, available in different food products and produces in small amounts in kidney and liver (Fig. 1). The healthy people can cover the daily requirement of arginine from food and synthesis, but in case of several pathologies arginine secretion in the body drops and the body can suffer from relative lack of the arginine.

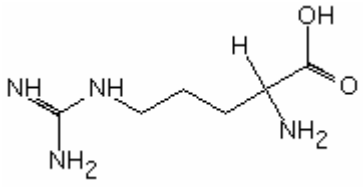

Fig. 1. **Chemical structure of L-arginine**

Arginine serves a number of important metabolic functions in addition to its well-recognized roles in the transport and excretion of nitrogen and as a substrate for protein synthesis. For example, it is an allosteric activator for the synthesis of N-acetylglutamate and this, in turn, activates carbamoyl-phosphate synthetase 1 (CPS-1), playing a role in the regulation of urea production. It donates an amidino group for the synthesis of guanidoacetic acid, which is a precursor of creatine. Also, via conversion of arginine to ornithine, it is involved in the synthesis of the polyamines and proline.

A relatively newly identified but important function of arginine is its precursor role in the formation of the free radical, nitric oxide (NO), which acts as a signal transducer, an endogenous vasodilator, and a cytotoxic molecule for invading microorganisms and tumor cells.

At high concentrations, free radicals and radical-derived, nonradical reactive species are hazardous for living organisms and damage all major cellular constituents. At moderate concentrations, however, NO, superoxide anion, and related reactive oxygen species (ROS) play an important role as regulatory mediators in signaling processes. Many of the ROS-mediated responses actually protect the cells against oxidative stress and reestablish "redox homeostasis."

Molecules with a certain asymmetry, or handedness, have an important role to play in living cells. This configuration of proteins can be changed by electromagentic excitation. When polarized electromagnetic waves are used, the rotational excitation of the atoms and molecules is markedly reduced or increased depending on its structure. Light or any other electromagnetic radiation at specific wavelengths, specific to the absorption spectra of the molecule, can force a change in the rotation of the molecule and thus activate an inactive dextrorotatory form into an active levorotatory form. L-Arginine has strong absorption maximas at 400-470nm, which is in the blue light region. Whereas D-Arginine has low reactivity in the blue field, but somewhat higher reactivity than L-Arginine in the yellow to red spectral areas (Fig. 2).

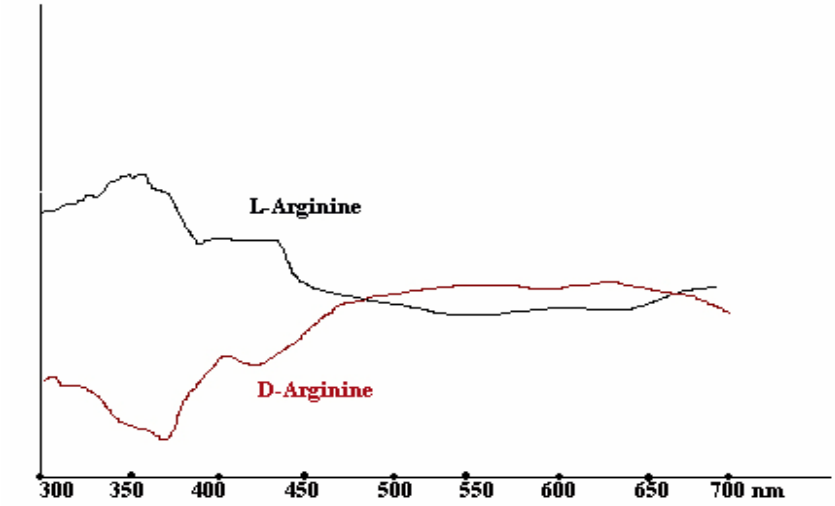

Fig 2. **Absorption spectra of L-Arginine and D-Arginine at pH 7.01**

Reactive Oxygen Species

Higher organisms have evolved the use of NO and ROS also as signaling molecules for number of physiological functions. These include regulation of vascular tone, monitoring of oxygen tension in the control of ventilation and erythropoietin production, and signal transduction from membrane receptors in various physiological processes. NO and ROS are typically generated in these cases by tightly regulated enzymes such as NO synthase (NOS) and NAD(P)H oxidase isoforms, respectively. In a given signaling protein, oxidative attack induces either a loss of function, a gain of function, or a switching to a different function. Excessive amounts of ROS

may arise either from excessive stimulation of NAD(P)H oxidases or from less well-regulated sources such as the mitochondrial electron-transport chain. In mitochondria, ROS are generated as undesirable side products of the oxidative energy metabolism. An excessive and/or sustained increase in ROS production has been implicated in the pathogenesis of cancer, diabetes mellitus, atherosclerosis, neurodegenerative diseases, rheumatoid arthritis, ischemia/reperfusion injury, obstructive sleep apnea, and other diseases. In addition, free radicals have been implicated in the mechanism of senescence

The NADPH oxidase of phagocytic leucocytes is the source of ROS that these cells need to kill invading pathogens. In recent years, numerous reports have produced evidence of a role for putative non-phagocyte NADPH oxidase(s) in the vascular production of ROS, because several of the components of the phagocyte NADPH oxidase have been detected in vascular tissue of several animal species, including humans. However, these studies suggest distinct differences in amino acid sequence (and antibody reactivity) between the central subunits of the phagocyte and non-phagocyte NADPH oxidase(s). ROS produced by these putative non-phagocyte NADPH oxidase(s) are involved in various (patho)physiological responses of vascular cells, such as mitosis, apoptosis, migration, hypertrophy, and modification of the extracellular matrix. Accordingly, ROS have been implicated in several major intracellular signalling pathways leading to changes in gene transcription and protein synthesis. The initial pathway for oxidant generation involves a membrane associated NADPH oxidase that reduces oxygen to superoxide anion [12], which then dismutates to form H_20_2.

ROS production by NAD(P)H oxidases in nonphagocytic cells

The production of ROS by nonphagocytic NAD(P)H oxidase isoforms plays a role in the regulation of intracellular signaling cascades in various types of nonphagocytic cells including fibroblasts, endothelial cells, vascular smooth muscle cells, cardiac myocytes, and thyroid cells [21,29,30,40,41,42,63,67]. In most of these cases, rac1 is involved in the induction of NAD(P)H oxidase activity [41,42,105]. Muscle cells and fibroblasts account for most of the superoxide produced in the normal vessel wall.

The NAD(P)H oxidase isoforms of the cardiovascular system are membrane-associated enzymes that appear to utilize both NADH and NADPH [30]. The rate of superoxide production in nonphagocytic cells is only about one-third of that of neutrophils. Vascular smooth muscle cells, in contrast to neutrophils, endothelial cells, or fibroblasts, generate superoxide and hydrogen peroxide mainly intracellularly.

The cardiovascular NAD(P)H oxidase isoforms are induced by hormones, hemodynamic forces, or by local metabolic changes [30]. Angiotensin II increases NAD(P)H-driven superoxide production in cultured vascular smooth muscle cells and fibroblasts. Thrombin, platelet-derived growth factor (PDGF), and tumor necrosis factor-α (TNF-α) stimulate NAD(P)H oxidase-dependent superoxide production in vascular smooth muscle cells. Interleukin-1, TNF-α, and platelet-activating factor increase NAD(P)H-dependent superoxide production in fibroblasts. Mechanical forces stimulate NAD(P)H oxidase activity in endothelial cells. Reoxygenation stimulates NAD(P)H oxidase activity in cardiac myocytes.

ROS production by phagocytic NADPH oxidase: the oxidative burst

Activated macrophages and neutrophils can produce large amounts of superoxide and its derivatives via the phagocytic isoform of NADPH oxidase. This enzyme is a heme-containing protein complex illustrated schematically in Figure 3. In an inflammatory environment hydrogen peroxide is produced by activated macrophages at an estimated rate of $2\text{-}6\times10^{-14}$ $mol\cdot h^{-1}\cdot cell^{-1}$ and may reach a concentration of 10-100 μM in the vicinity of these cells [43, 54, 73]. The massive production of antimicrobial and tumoricidal ROS in an inflammatory environment is called the "oxidative burst" and plays an important role as a first line of defense against environmental pathogens. The physiological relevance of NADPH oxidase as a defense agent is suggested by the observation that mice lacking the NADPH oxidase components $gp91^{phox}$ or p47

exhibit reduced resistance to infection [17, 18, 24, 70, 80, 84, 90]. The combined activities of NADPH oxidase and myeloperoxidase in phagocytes leads, in addition, to the production of hypochlorous acid (HClO), one of the strongest physiological oxidants and a powerful antimicrobial agent [34, 87]. Stimulated neutrophils and macrophages generate also singlet oxygen by reactions that involve either myeloperoxidase or NADPH oxidase [94]. Importantly, however, physiologically relevant ROS concentrations can also modulate redox-sensitive signal cascades and enhance immunological functions of lymphocytes.

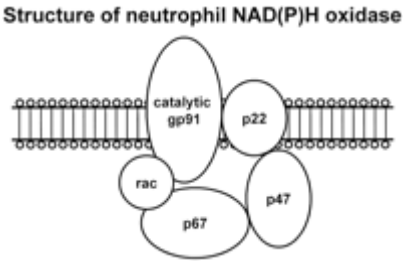

Fig. 3. **Structure of neutrophil NAD(P)H oxidase. The enzyme consists of the membrane-bound cytochrome b_{558} complex comprising gp91^{phox} and p22^{phox}, the cytosolic proteins p47 and p67, and a low-molecular-weight G protein of the rac family.**

Phagocytic NADPH oxidase becomes activated upon translocation of cytosolic p47, p67, and a G protein of the rac family to the membrane-bound cytochrome b_{558} complex that contains gp91^{phox} and p22 (Fig. 3). The activation of phagocytic NADPH oxidase can be induced by microbial products such as bacterial lipopolysaccharide, by lipoproteins, or by cytokines such as interferon-γ, interleukin-1β, or interleukin-8 [5]. The activation of NADPH oxidase is mainly controlled by the rac isoform rac2 in neutrophils and rac1 in macrophages and monocytes [58, 97].

Myeloperoxidase, a secreted heme protein, amplifies the toxic potential of H_20_2 by producing reactive intermediates. Production of myeloperoxidase is inhibited by irradiation at 633 nm, 660 nm, 820 nm, 880 nm and 950 nm, of which 660 nm appears to have the strongest effect [15, 36, 46, 47, 99].

The major product of myeloperoxidase at plasma concentrations of chloride ion is hypochlorous acid (HOCl). This potent cytotoxin chlorinates electron rich substrates and oxidatively bleaches heme proteins, nucleotides and carotenoids. Indirect evidence suggests that reactive carbonyls form in proteins and amino acids exposed to myeloperoxidase-generated HOCl, and trace quantities of aldehydes have been detected in amino acids exposed to high concentrations of reagent HOCl under strongly acidic conditions.

The amino acids L-Serine and L-threonine are both present in concentrations up to 200 microM in plasma suggesting that hydroxy-amino acids may be substrates for oxidation by myeloperoxidase in vivo. Myeloperoxidase is a component of human atherosclerotic lesions and the patterns of immunostaining for the enzyme and for HOCl modified proteins are remarkably similar to those reported for oxidation-specific epitopes in rabbit atherosclerotic lesions. A wealth of evidence indicates that LDL, the major carrier of cholesterol in humans, must be oxidized to trigger the pathological events of atherosclerosis. LDL isolated from human aortic tissue exhibits immunoreactivity with polyclonal antibodies specific for acrolein modified proteins. These observations suggest that myeloperoxidase may be a catalyst for LDL oxidation in vivo, and that acrolein generated by myeloperoxidase may play a role in converting LDL into an atherogenic particle.The high yield of the L-serine and L-threonine oxidation products suggests that other free amino acids may be substrates for oxidation by myeloperoxidase. The total concentration of free amino acids, including L-arginine, in plasma is [approximately] 4 mM, suggesting that reactive aldehydes derived from amino acids may be major products of phagocyte activation in vivo.

It has been demonstrated that an enzyme, superoxide dismutase (SOD), specifically catalyses the dismutation of superoxide and that its radical, if its concentration is elevated, may react with hydrogen peroxide to form a much more reactive hydroxyl radical.
The function of SOD can be regulated by activating the redox sites of copper and zinc or iron and manganese by their absorption maxima at 404 nm, 450 nm, 584 nm, 620 nm, 632 nm, 680 nm, 685 nm, 760 nm, 780 nm or 820 nm.
Klebanov [2003] found that lipopolysaccharides increased NO production and SOD activity in macrophages in a concentration-dependent manner. The irradiation of macrophages by red light resulted in a dose-dependent increase in NO production and SOD activity. The incubation of irradiated cells in the presence of 10 microM cycloheximide abolished the increase. The presence of antioxidants (mexidol and ascorbate) also significantly inhibited the laser-induced activity of macrophages. Thus, laser irradiation of cells in the red range activates the synthesis of SOD and inducible NO-synthase de novo due to photosensitized initiation of free radical reactions.

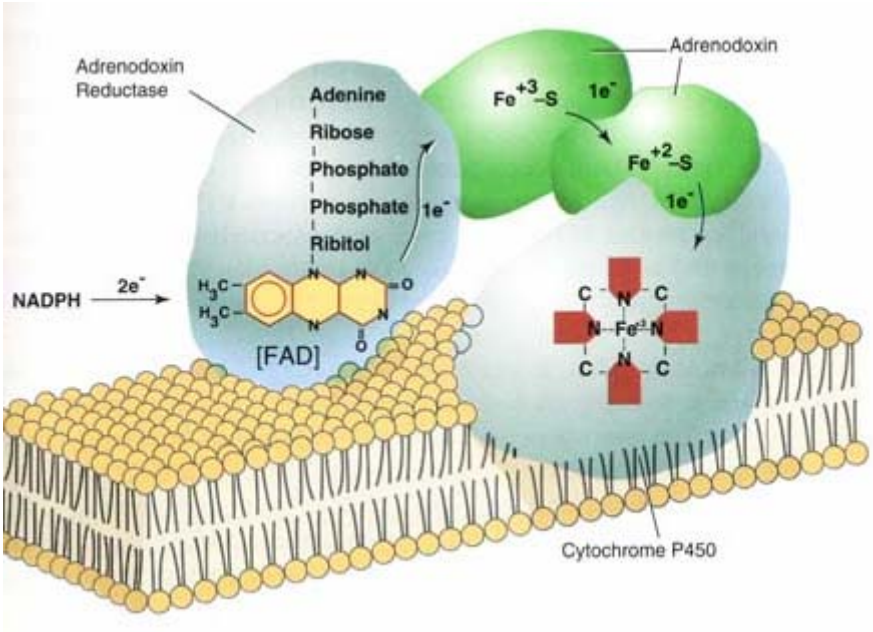

Fig. 4. **Structure of cytochrome P450**

Superoxide can reduce oxidized cytochrome c

$$O_2^- + \text{cyt c}(Fe^{3+}) \rightarrow O_2 + \text{Cyt c}(Fe^{2+})$$

or be removed by the presence of the specific enzyme superoxide dismutase. In this reaction, superoxide acts as both oxidant and reductant. The chemical effects of the superoxide free radical in the tissues are amplified by its giving free rise to free radical chain reactions. It has been proposed that O_2^- bound to cytochrome P450 (Fig. 4) is an intermediate in the activation of oxygen in hydroxylation reactions. The function of superoxide dismutase is to catalyze the dismutation of superoxide to oxygen and water:

$$O_2^- + O_2^- + 2H^+ \rightarrow O_2 + H_2O$$

NADPH and NO

Distinct enzymes are involved in NO formation in different cell types, each of them utilizing NADPH as a cofactor. NOS-I, found primarily in central and peripheral neuronal cells is constitutive Ca^{2+}-, calmodulin-, and NADPH-dependent. It synthesizes NO through a transduction mechanism to regulate the activity of soluble guanylate cyclase. Immunohistochemistry with anti NOS-I antibodies revealed NOS-I in neurons, within the brain and spinal cord. NOS-II is induced in macrophages and other cells by endotoxin and some cytokines. It is Ca^{2+} independent and requires NADPH and tetrahydrobiopterin.

The inducible isoform of NO synthase (iNOS) is produced in macrophages, hepatocytes, vascular smooth muscle cells and endothelium in response to endotoxin, cytokines and other proinflammatory factors.

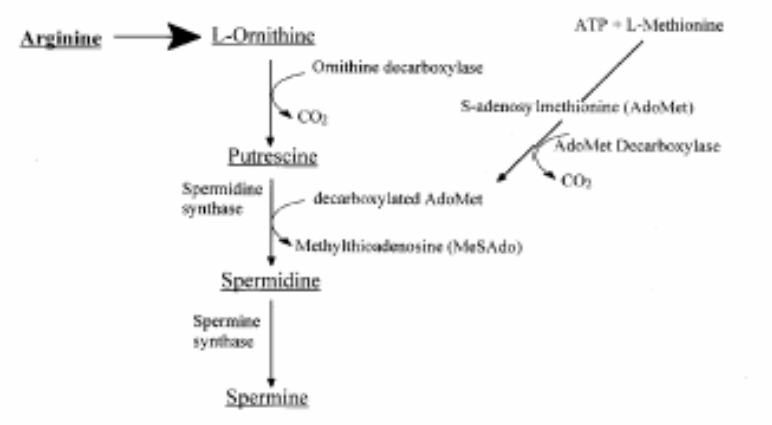

Fig. 5. **Arginine breakdown**

An additional role played by arginine is in the process of tissue protein breakdown. Thus, arginyl-tRNA is involved in the posttranslational conjugation of arginine to acidic amino terminals of proteins, a step that is required for their degradation via the ubiquitin-dependent pathway. Indeed, the existence of two forms of arginyl-tRNA synthase in rat liver has been reported. One is a free protein which is thought to be involved in this conjugation process that is associated with protein degradation. The other form is a component of a high molecular weight complex which provides the arginyl-tRNA for polyribosome directed polypeptide synthesis. This is molecular evidence for the channeling of arginine within cells and, thus, a subcellular compartmentation in its metabolism.

Production of L-arginine is regulated by several factors. L-arginine is produced from citrulline in the kidney cells and ornithine in the liver cells. Activation of carbamoyl phosphate synthetase will also produce arginine from glutamate through the carbamoyl-phosphate pathway. Glutamate reacts strongly to 537 nm and 712nm, 806 nm, 865 nm and 945 nm wavelengths.

Arginine, when infused systemically, produces vasodilation and increases in glomerular filtration ratio (GFR). Since the discovery of NO, it has been primarily assumed that arginine induced renal vasodilation is mediated by the generation of NO from arginine. Arginine to NO production can be triggered by light at 350 nm, 420-470 nm, 760 nm and to a lesser degree by wavelengths in the red visible region. Other amino acids which produce vasodilation, such as glycine, have been shown to be NO dependent [32, 36]. Studies have demonstrated that animals pretreated with L-NMMA, a NOS inhibitor, exhibit decreased plasma flow and modest reductions in nephron filtration rate, but when arginine is infused, nephron filtration rate increases, often to supranormal values. When one infuses glycine or other vasodilatory amino acids after pre-treatment with L-NMMA, no increase in GFR occurs, data which are interpreted in support of NO dependence of these phenomena [1, 2, 36, 38].Recent studies following arginine infusion demonstrated that the increase in GFR observed after arginine infusion required the activity of arginine decarboxylase in that infusion of the compound, DFMA (di-fluoro-methyl-arginine), an inhibitor of arginine decarboxylase, prevented the increase in GFR following arginine infusion, whereas, inhibition of NOS did not prevent the changes in GFR (Fig. 1). These data suggest that the vasodilation and increase in GFR following systemic arginine infusion do not require the activity of NOS but that arginine-induced vasodilation does require the activity of arginine decarboxylase via, presumably, the generation of agmatine. These events may also require the participation of insulin release.

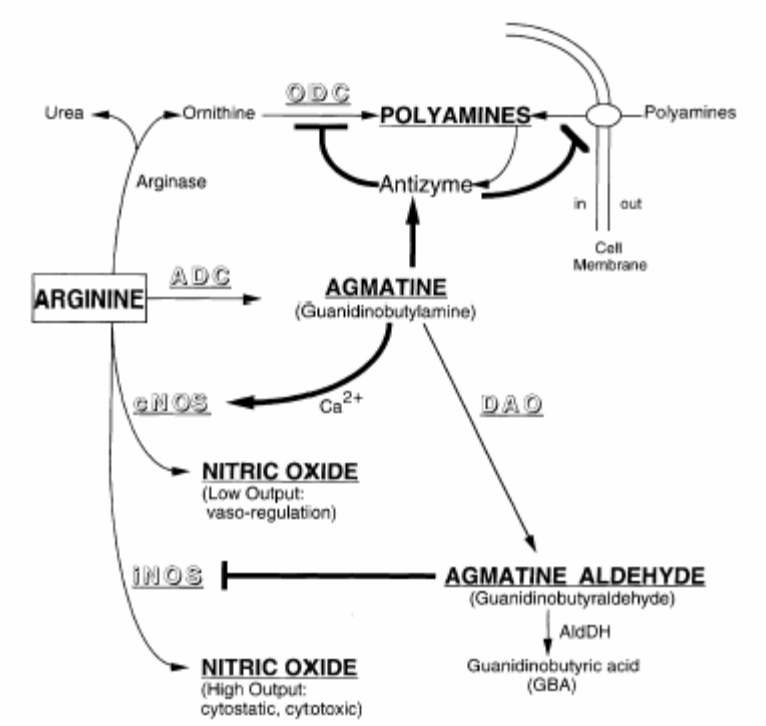

Fig. 6. **Arginine, NO and agmatine pathways**

L-arginine has also been shown to be the unique substrate for the production of agmatine (Fig. 6). Agmatine has potential as a treatment of chronic pain, addictive states and brain injury. It also competitively inhibits the activity of all isoforms of nitric oxide synthase, protecting the body from excess effects of NO. This reaction can be regulated by cytochrome P450 and light at 450 nm, cytochrome a gamma with light at 436 nm (Fig. 7, 8), and cytochrome α (alpha) with light at 630 nm. Recent evidence suggests that agmatine, which is an intermediate in polyamine biosynthesis, might be an important neurotransmitter in mammals.

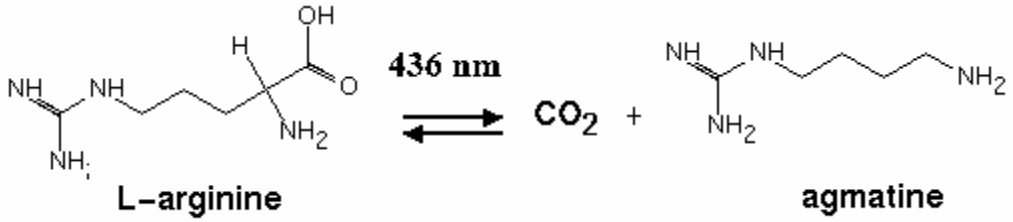

Fig. 7. **Arginine to agmatine reaction**

Recently, agmatine, decarboxylated arginine, has been demonstrated to be an important biological compound in several tissues, and is synthesized by arginine decarboxylase. NO and agmatine not only produce vascular effects but also appear to contribute to the regulation of cell proliferation.

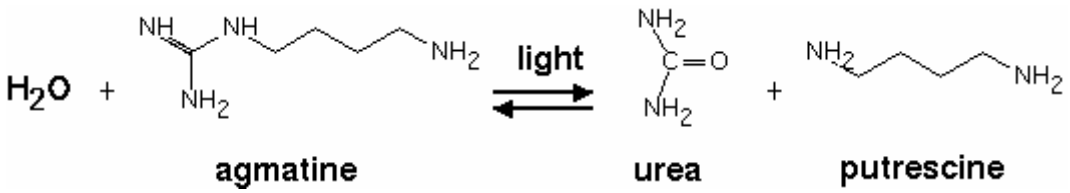

Fig. 8. **Arginine to urea and putrescine reaction**

Later studies have also suggested that agmatine causes increases in intracellular calcium in endothelial cells. It has also been demonstrated that inhibition of NOS prevents the increase in nephron filtration rate during the infusion of agmatine, implying NO dependence of this phenomenon [88], which seems at first glance to be internally contradictory to the observations noted above. NO may also exert effects by inhibition of certain P450 enzymes which generate products from arachidonic acid There are further studies which shed more light on the mechanism whereby agmatine produces renal vasodilation and increases in GFR [Peterson et al. 1998]. Other recent studies have suggested that there are important intracellular pools of calcium which are not sensitive to IP3 but rather utilize calcium-induced calcium release mechanisms. The ryanodine receptor channel has been known to be important for calcium release in non-vertebrate such as sea urchins [Lee 1997]. Recent studies have also suggested that this ryanodine receptor, calcium-induced calcium release mechanism may be quite important in mammals as well [Marks 1997]. The ryanodine receptor channel appears to be regulated by the generation of an NAD metabolite, cyclicADP-ribose (cADP-ribose) via the enzyme ADP-ribose cyclase. Peterson et al, [1998], examined the mechanisms of vasodilation and the increase in GFR observed after agmatine utilizing 8-bromo-cADPribose, an inhibitor of the activity of cADP-ribose, an agent which enhances the sensitivity of the ryanodine receptor calcium release mechanism

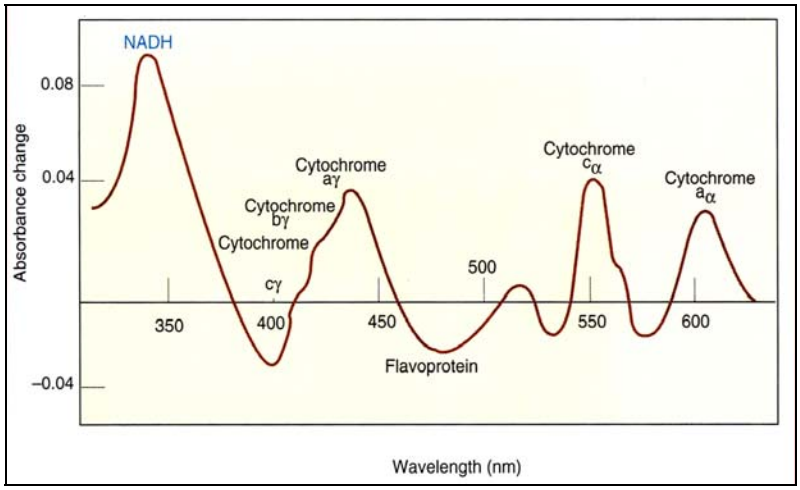

Fig. 9. **Absorption spectra of cytochromes**

NO is formed from L-arginine by oxidation of its guanidino-nitrogen terminal by NO synthase. NO synthase is primarily a cytosolic enzyme requiring calmodulin, Ca2+, α-nicotinamide-adenine dinucleotide hydrogen phosphate (NADPH), and tetrahydrobiopterin, and has similarities with cytochrome P450 enzymes. These all have absorption maxima between 446 nm and 652 nm (Fig. 9). Several isoforms of the enzyme occur in endothelial cells, as well as in platelets, macrophages, vascular smooth muscle cells, and the brain

Stem cells

By suppressing the activity of NO synthases (NOS), it is possible to increase the number of stem and progenitor cells in the bone marrow (BM) Hematopoietic stem cells give rise to various multipotent progenitor populations, which expand in response to cytokines and which ultimately generate all of the elements of the blood.

Cells produced by the hematopoietic system of the adult organism originate from rare pluripotent hematopoietic stem cells that reside in the BM [101, 71]. In contrast to the rapid division of progenitor cells, the proliferative activity of hematopoietic stem cells in the BM is restricted [98, 15, 66, 15,12 and 38]. The relative quiescence of the pool of stem cells and its resistance to cytokine signaling may be crucial for preventing the premature depletion of the stem cell

compartment during stressful conditions. The signaling systems that control the pool of hematopoietic stem cells are poorly understood, and so far only a handful of regulators of hematopoietic stem cells has been described p27(kip1), p21cip1/waf1, HoxB4, Bmi-1 [12, 13, 3, 50, 57, 77].

NO, a multifunctional signaling molecule [38], can induce gene expression, affect multiple signaling pathways, and act as a potent antiproliferative factor in a variety of cells; thus, it may potentially contribute to the homeostasis of the stem cell pool. Expression of various NO synthase (NOS) isoforms has been reported in human and rodent BM and blood [26]: for instance, iNOS RNA can be detected in megakaryocytes, eosinophils, and unstimulated monocytes [100, 2]; eNOS RNA has been found in platelets, megakaryocytes, and lymphocytes [85, 11]; and nNOS RNA has been detected in neutrophils [100, 11, 27]. Furthermore, inhibitory action of exogenous NO donors on *in vitro* colony growth of various subpopulations of BM cells has been demonstrated for human BM cells; for instance, NO donors can markedly decrease production of myeloid and erythroid colonies by $CD34^+$ cells [65, 89]. Moreover, NO may mediate the action of some cytokines (e.g., TNF-α and IFN-γ) *in vitro* [65, 82].

It has been shown that inhibition of NOS activity *in vivo* results in an increase in the number of stem and early progenitor cells in the BM. Moreover, it has been demonstrated that this increase in the number of stem cells is followed by an increase in the neutrophil content in the blood. These results point to NOS as an important regulator of hematopoietic stem cells and indicate that it may be possible to expand the number of cells in the stem cell pool by suppressing the activity of NOS [82, 25].

There are numerous observations, both *in vitro* and *in vivo*, that support a role for NO in negative regulation of stem cell division. NO has been shown to mediate the action of growth factors and to control the balance between proliferation and differentiation in cultured cells, including neuronal and endothelial cells, cardiomyocytes, adipocytes, and osteoblasts [25]. It has been also demonstrated that exposure to chemical donors of NO can change the extent of hematopoietic maturation *in vitro* [65, 89] and that NO mediates the action of TNF-α, IFN-γ, and GM-CSF on hematopoietic cells *in vitro* [65, 89, 82, 83]. *In vivo*, NO has been shown to act as an essential antiproliferative signal during *Drosophila* disc development [48, 49, 102], moth neurogenesis [10], and *Xenopus* brain development [79], as well as in the adult mammalian brain [76,14, 69]. Thus, in a variety of contexts, NO may be acting as a reversible "damper" to slow down or arrest the cell cycle. This activity of NO may overlap with another recently described role for NO in another hematopoiesis-related process, the mobilization of stem and progenitor cells to the PB [1].

Potential effectors of NO in the BM may include the cyclin-dependent kinase inhibitor p21WAF1: in the absence of p21, proliferation of hematopoietic stem cells is increased [12, 13], and NO is known to induce p21WAF1 expression in several systems [81, 39, 72, 33, 36]. Other effectors of NO signaling might include HOXB4 or Bmi-1, which were recently described as critical regulators of stem cells pools in animals [3, 50, 57, 77]. Yet another possible link between NO and hematopoiesis may emerge from the potential of NO to regulate proteolysis and, thus, to affect the mobilization of stem cells or their interaction with the stromal cells in the BM [1, 35]. The mechanistic link between NO and hematopoiesis may involve, more generally, modification of the activity of proteins [94, 44], redox regulation [44, 103], and resetting gene expression patterns in the cell by activating multiple signaling pathways [36]; thus, suppression of NOS activity may induce profound changes in hematopoietic stem cells and increase their self-renewal or survival potential.

Although the primary function of stem cell factor (SCF) in early hematopoiesis might be to induce the growth of quiescent progenitor/stem cells through synergistic interactions with other early-acting cytokines, ample evidence indicates that SCF, in the absence of other cytokines, selectively promotes viability rather than proliferation of primitive murine progenitor cells[26] Although SCF/c-kit migratory pathways and developmental fates are well documented, less is known about the molecular mechanisms that provide biologic specificity to the SCF/c-kit

signaling pathway in the formation and migration of c-kit$^+$ cells. c-Kit is a receptor tyrosine kinase (RTK), which constitutes a type III RTK subfamily with the receptors for platelet-derived growth factor (PDGF), colony-stimulating factor 1 (CSF-1), and flt-3 ligand.
These biologic events controlled by the SCF/c-kit signaling pathway are reminiscent of those that take place in epithelial-mesenchymal transitions during mammalian development. Indeed, the process of mesoderm formation involves the acquisition of migratory properties and cell fate determination. These epithelial-mesenchymal transitions are controlled by a conserved family of zinc-finger proteins, which have light absorptioption maxima at 404 nm, 450 nm, 584 nm, 633 nm, 680 nm, 685 nm and 780 nm.

Summary

NO is formed from L-arginine by oxidation of its guanidino-nitrogen terminal by NO synthase. NO synthase is primarily a cytosolic enzyme requiring calmodulin, Ca^{2+}, α-nicotinamide-adenine dinucleotide hydrogen phosphate (NADPH), and tetrahydrobiopterin, and has similarities with cytochrome P450 enzymes. These all have absorption maxima between 446 nm and 652 nm. Several isoforms of the enzyme occur in endothelial cells, as well as in platelets, macrophages, vascular smooth muscle cells, and the brain. L-arginine has also been shown to be the unique substrate for the production of agmatine. Agmatine has potential as a treatment of chronic pain, addictive states and brain injury. It also competitively inhibits the activity of all isoforms of nitric oxide synthase, protecting the body from excess effects of NO. This reaction can be regulated by cytochrome P450 and light at 420 - 470nm, cytochrome a gamma with light at 436nm, and cytochrome a alpha with light at 630 nm. Recent evidence suggests that agmatine, which is an intermediate in polyamine biosynthesis, might be an important neurotransmitter in mammals. Agmatine is synthesized in the brain, stored in synaptic vesicles in regionally selective neurons, accumulated by uptake, released by depolarization, and inactivated by agmatinase. Agmatine binds to alpha2-adrenoceptors and imidazoline binding sites, and blocks NMDA receptor channels and other ligand-gated cationic channels. Furthermore, agmatine inhibits nitric oxide synthase, and induces the release of some peptide hormones. As a result of its ability to inhibit both hyperalgesia and tolerance to, and withdrawal from, morphine, and its neuroprotective activity, agmatine has potential as a treatment of chronic pain, addictive states and brain injury and protects against the harmful effects on excess NO. It is proposed that the regulation of L-arginine turnover by the use of light at blue wavelengths between 400 and 510 nm can be the explanation for the observed effects of blue light: lowering of blood pressure, pain killing effect, regulating insulin production, anti-inflammatory action, and possible effects on the release of stem cells.

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