Nitric Oxide

by Jeff Golini

Nitric Oxide:

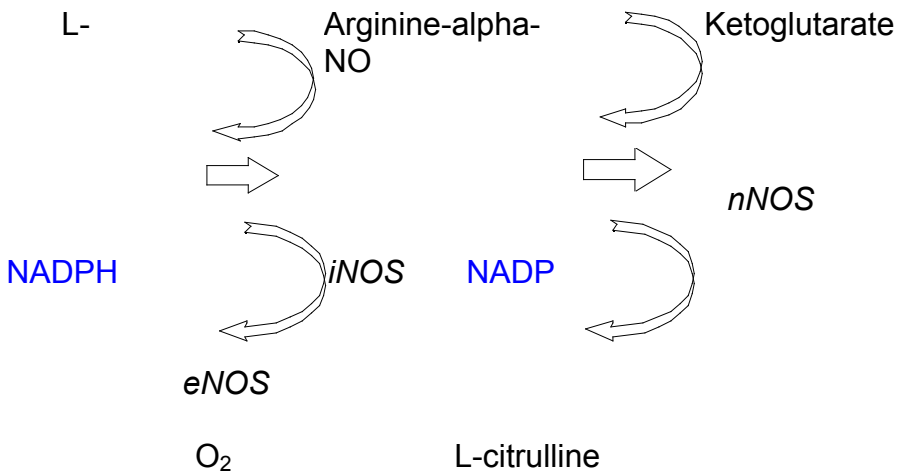
Nitric Oxide (NO) is a very important signaling molecule that acts in many tissues to regulate a wide range of physiological processes. It was first discovered several years ago by a group that was attempting to identify the agent responsible for promoting blood vessel relaxation and the regulation of vascular tone. This particular agent was named endothelium-derived relaxing factor (EDRF), and was initially assumed to be a protein like most of the other signaling factors previously discovered. The discovery that EDRF was in fact nitric oxide, a small gaseous molecule, has led to many publications over the years including our NOS™ discovery. Our scientist found that besides promoting blood vessel relaxation and the regulation of vascular tone, NO plays a key role in many biological processes including immune defense, neurotransmission, and the regulation of cell death (apoptosis). Since NO is such a very small molecule, it is able to diffuse rapidly across cell membrane and depending on the conditions, is able to travel several hundred microns. Nitric oxide is produced by enzymes known as nitric oxide syntheses (NOS).

Nitric Oxide Syntheses:

Nitric Oxide (NO) is produced by a group of enzymes called nitric oxide syntheses (NOS). These enzymes (present in body) convert the Arginine in our Arginine alpha-Ketoglutarate (AKG) into citrulline, producing NO in the process. Oxygen and NADPH are necessary co-factors. The pure and simple science starts with the correct form of AKG.

There are three isoforms of NOS which have been named according to their activity. They are neuronal NOS (nNOS), endothelial NOS (eNOS), and inducible NOS (iNOS). Our scientists commonly refer to these enzymes by number so that nNOS is known as NOS1, iNOS is NOS2, and eNOS is NOS3. Although there are three names, these isoforms can be found in a variety of tissues and cell types working toward the same biological functions. The general function of NO production from NOS is illustrated below in figure 1.

Figure 1:



nNOS & eNOS synthesizes nitric oxide in response to intracellular calcium levels. In other words, like all NOS isoforms, its activity is dependent on the binding of calmodulin. Increases in cellular calcium leads to increases in levels of calmodulin and the increased binding of calmodulin to eNOS and nNOS which then leads to an increase in NO production by these enzymes. The binding of calmodulin is required for the activity of all the NOS isoforms to convert our Arginine alpha-Ketoglutarate to nitric oxide.

Physiological Roles of Nitric Oxide:
Since the initial discovery that NO is able to induce vasodilation, a large number of other roles have also been found, as described below.

Role in immune system: NO can be produced by numerous cells involved in immune response. In particular cytokine-activated macrophages can produce high levels of NO in order to kill targeted cells such as tumors and bacteria.

Role in inflammation: NO has shown to act as a mediator of inflammatory processes. This process has enhanced the effect of cyclooxygenases and stimulates the production of pro-inflammatory eiconosoids.

Role in nervous system: NO behaves as a neurotransmitter in the central and peripheral nervous systems, and because of this function, is has shown to be involved in regulating apoptosis in neurons.

Role in blood flow: NO relaxes the smooth muscle in the walls of the arterioles. At each systole, the complex endothelial cells that line the blood vessels, will release a puff of NO, which then diffuses into the underlying smooth muscle cells. This process causes these cells to relax, which permits the surge of blood to pass through easily.

L-Arginine-alpha-Ketoglutarate:
This amino acid compound was discovered by Rocky Mountain Chemical Company (RMC), back in the 1980's, as being a superior form for delivering L-Arginine to the human system. RMC is the only domestic manufacture for this compound, along with 21 other amino acids that are bound to alpha-Ketoglutarate.
Our research scientist discovered that L-Arginine-alpha-Ketoglutarate was a fuel for nitric oxide synthases (NOS). In laymen's terms, we discovered a natural, non-drug method of creating nitric oxide in the human body. This mechanism is complex, but the trigger-mechanism is very elemental. In order to stimulate or produce nitric oxide in the body, a terminal nitrogen atom must combine with an oxygen molecule in the blood. An enzyme called nitric oxide synthase controls this reaction and NADPH (a niacin-containing redox-active electron storage compound), mediates the reaction. The reaction is accomplished and controlled by oral ingestion of L-Arginine-alpha-Ketoglutarate. The left-handed molecule, called L-Arginine, is the primary source for nitric oxide in humans. When NO is produced in the body by this process, scientists have referred to this as ADNO or Arginine-Derived-Nitric-Oxide.
Additional clinically proven benefits of pure Arginine are:
*Improved blood flow in men with elevated serum cholesterol and early coronary artery disease.

Circulation

*Reduced pathological increases in the thickness of plaque-lined walls in people with elevated cholesterol.

*Lowered plasma cholesterol levels in subjects with advanced hypertension.

New England Journal of Medicine

*Elderly patient's oral treatments resulted in significant improvement in lipid profiles, with no side effects.

Journal of Perenteral & Enternal Nutrition

*Enhanced coronary artery blood flow in heart patients.

Journal of the American College of Cardiology

*Improved blood-vessel relaxation

Circulation

L-Arginine-alpha-Ketoglutarate has several other important functions besides the above. Remember biology 101, which taught that this compound is essential to the metabolism of ammonia that is generated from protein breakdown and the transportation of nitrogen used in muscle metabolism. L-Arginine also influences several hormone functions, like the stimulation to the pituitary gland for the production of growth hormone. Human growth hormone helps in muscle building, leading to increased muscle size, strength, tone, along with strengthening tendons and ligaments. Growth hormone, in general, decreases body fat and increases metabolism which results in more energy. Back in the 1980's a book called *Life Extension* (Pearson & Shaw) proved that adequate amounts of the amino acid L-Arginine did stimulate growth hormone production.

References:

1).Barbul, Fishel, Shimazu, Wasserkrug, Yoshimura, Tao, And Efron, Intravenous Alimentation with High Arginine levels Improves Would Healing and Immune Function., Journal of Surgical Research, 38 (1985), 228-334.

2).Jay Lombard, board Certified Neurologist; The Brain Wellness Plan, Breakthrough Medical, Nutritional, and Immune-Boosting Therapies, 1998.

3). Bath PMW, Willmont M, Leonardi-Bee, Bath FJ, Nitric oxide donors, L-Arginine, or nitric oxide synthase inhibitors for acute stroke, Cochrane Review, March 2002.

4).R.M.J. Palmer, A.G. Ferrige, S. Moncada, "Nitric Oxide release accounts for the biological activity of endothelium-derived relaxing factor," Nature, 327:524-526, 1987.

5). S. Monada, R.M.J. Palmer, E.A. Higgs, "Nitric oxide-physiology, pathophysiology, and pharmacology," Pharmacological Reviews, 43:109-142, 1992.

6). R.M.J. Palmer, D.S. Ashton, S. Monada, "Vascular endothelial cells synthesize nitric oxide from l-Arginine," Nature, 333:664-666, 1988.

7).Monada, S. , Higgs A., "The L-Arginine-nitric oxide pathway, New England J. Med, 329:2002-2012, 1993.

8).Hishikawa, Nakaki, Tsuda, Esumi, Ohshima, Suzuli, Saruta and Kato, Effect of Systemic L-Arginine administration on hemodynamis and nitric oxide release in men, Japan Heart Journal, 33:41-48, 1992.

9).1998 FDA Public records department.

10).M.W. Radomski, S. Moncada, R.M.J. Palmer,"The role of nitric oxide and cGMP in platelet adhesion to vascular endothelium," Biochem. Biophys. Res. Comml, 148:1482-1489, 1987.

11).S.Moncada, "L-Arginine-nitric oxide pathway," Acta Physiological Scandinavia, 145:201-227, 1992.

12).M.R.Shaffer, U. Tatry, R.A. Van Wesep, A. Brabul, "Nitric oxide metabolism in wounds. Journal Surgical Res, 71:25:31, 1997.

13).Schmidt, Hofman, Shindler, Shutenkl, "NO from NO synthases, Proc Nati Aad Sil, 93:14492-14497, 1997.

14).D. D. Rees, R.M.J. Palmer, S. Moncads, "Role of endothelium-derived nitric oxide in the regulation of blood pressure", Proceedings of the National Academy of Sciences, 86:3375-3378, 1989.

15).R.J. Gryglewski, S. Moncada, R.M.J. Palmer, "Superoxide anion is involved in the breakdown of endothelium-derived vascular relaxing factor", Nature, 320:454-456, 1986.