

Nutritional Regulation of NO Synthesis and Its Implications for Health

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Nitric oxide (NO) is synthesized from L-arginine by NO synthase (NOS) in virtually all mammalian cells in the presence of Ca^{2+} , tetrahydrobiopterin (BH₄), O₂, NADPH, FAD, FMN, and calmodulin (1). There are three isoforms of the NOS: nNOS (originally identified in neuronal tissue; type I), iNOS (originally identified as being inducible by cytokines; type II), and eNOS (originally identified in endothelial cells; type III). nNOS and eNOS, which require Ca^{2+} for their catalytical activities, are collectively term constitutive NOS. A quantitatively small amount of NO is produced by eNOS and nNOS in mammalian cells, whereas much larger amounts are generated in response to inflammatory cytokines and endotoxin. Because either a deficiency or an excess of NO production can result in dysfunction of cells and tissues, understanding the role for diet in regulating NO synthesis is crucial to maintaining health and preventing disease in humans and animals.

Increasing evidence over the past 15 years shows that a wide array of dietary factors, which include amino acids, glucose, fructose, cholesterol, fatty acids, vitamins, minerals, phytoestrogens, ethanol, and polyphenols, affect constitutive and inducible NO production in mammalian cells (1,2). Of note, the effects of these factors are cell- and tissue-specific, and concentration-dependent (Tables 1 and 2). There is growing recognition that changes in arginine transport, NOS activity, and intracellular levels of arginine, Ca^{2+} , BH₄ and NADPH are responsible for changes in NO synthesis in cells. Emerging evidence also shows that dietary factors can regulate NOS activity at the levels of gene transcription and/or translation. Most recently, much attention is directed towards identifying the role of BH₄ in enhancing endothelial NO production and reducing vascular oxidative stress.

Table 1. Effect of dietary factors on constitutive NO synthesis

| Dietary factor | Effect | Cell type | Effector(s) |
|---------------------|--------|--------------------------|-------------------------------|
| ω -3 PUFA | ↑ | EC & VSMC | eNOS, Ca & NADPH |
| ω -6 PUFA | ↑ | EC & VSMC | eNOS, BH ₄ & NADPH |
| ω -9 PUFA | ↓ | EC & VSMC | eNOS |
| Arginine | ↑ | Virtually all cell types | eNOS & BH ₄ |
| Ca^{2+} | ↑ | EC | eNOS |
| Carotenoids | ↑ | EC | BH ₄ |
| Cholesterol | ↓ | EC | eNOS & BH ₄ |
| Citrulline | ↑ | EC, neurons & VSMC | Arginine availability |
| Copper | ↓ | Glial cells | nNOS |
| Ethanol (chronic) | ↓ | EC | eNOS & BH ₄ |
| Ethanol (high) | ↓ | EC & brain | eNOS & nNOS |
| Ethanol (moderate) | ↑ | EC | eNOS |
| Flavonoids | ↑ | Vascular tissue | eNOS, BH ₄ & NADPH |
| Fiber (fermentable) | ↓ | Colon | cNOS |
| Folic acid | ↑ | EC | BH ₄ |
| Fructose | ↓ | EC | eNOS & BH ₄ |
| Glucosamine | ↓ | EC | NADPH |

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|--------------------|---|-------------------------|---------------------|
| Glucose (high) | ↓ | VSMC & mesangial cells | BH4 and glucosamine |
| Glucose (high) | ↑ | Neuronal cells | nNOS |
| Glutamate | ↑ | Brain | nNOS |
| Glutamine | ↓ | EC | NADPH |
| HDL | ↑ | EC | eNOS & BH4 |
| High-fat diet | ↑ | Kidney | eNOS |
| High-fat diet | ↓ | EC & neuronal tissue | eNOS & nNOS |
| High-glucose diet | ↑ | EC | eNOS |
| High-salt diet | ↓ | EC & kidney | eNOS & nNOS |
| Homocysteine | ↓ | EC, platelets & kidney | eNOS |
| Iron | ↑ | Gallbladder & intestine | eNOS & nNOS |
| LDL (oxidized) | ↓ | EC | eNOS & BH4 |
| Lead | ↑ | Brain | nNOS |
| Lysine | ↓ | EC & VSMC | Arginine transport |
| Magnesium | ↑ | EC | eNOS |
| Manganese | ↑ | Astrocytes & brain | nNOS & NADPH |
| Melatonin | ↓ | Brain | nNOS |
| Phytoestrogens | ↑ | Aorta & vasculature | eNOS & NADPH |
| Polyphenols | ↑ | EC | eNOS |
| Protein deficiency | ↓ | EC, kidney, muscle | eNOS & Arginine |
| Red wine | ↑ | EC | eNOS expression |
| Sphingolipids | ↑ | EC | eNOS |
| Taurine | ↑ | EC | eNOS & BH4 |
| VLDL | ↓ | EC | eNOS activity |
| Vitamin A | ↑ | EC & neuronal cells | eNOS & nNOS |
| Vitamin C | ↑ | EC | BH4 |
| Vitamin E | ↑ | EC | eNOS & BH4 |
| Zinc (high levels) | ↓ | Brain, EC & VSMC | nNOS & eNOS |

EC, endothelial cells; (V)LDL, (very) low-density lipoprotein; PUFA, polyunsaturated fatty acids; VSMC, vascular smooth muscle cells. ↑, increase; ↓, decrease.

Table 2. Effect of dietary factors on inducible NO synthesis

| Dietary factor | Effect | Cell type | Effector(s) |
|------------------|--------|---------------------|--------------------|
| ω-3 PUFA | ↓ | Macrophages | iNOS transcription |
| Arachidonic acid | ↓ | Macrophages | iNOS transcription |
| Arginine | ↑ | Astrocytes | iNOS translation |
| Cadmium | ↓ | Macrophages | iNOS expression |
| Carotenoids | ↓ | Macrophages | iNOS expression |
| Ceramide | ↑ | Macrophages | iNOS expression |
| Chromium | ↓ | Macrophages | iNOS expression |
| CLA | ↓ | Tumor cells | iNOS transcription |
| Cobalt | ↑ | Macrophages | iNOS expression |
| Copper | ↑ | Lung, liver & aorta | iNOS expression |
| Copper | ↓ | Macrophages | iNOS expression |
| Ethanol (high) | ↓ | Macrophages | iNOS activity |
| Fructose | ↓ | Macrophages | iNOS activity |

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|--------------------|---|------------------------|--------------------|
| Fructose | ↑ | Kidney | iNOS activity |
| Ginseng | ↑ | Macrophages | iNOS expression |
| Glucosamine | ↓ | Macrophages, lung & GI | iNOS expression |
| Glucose (high) | ↓ | Macrophages & kidney | iNOS/BH4 |
| Glucose (high) | ↑ | Heart & retinal cells | iNOS expression |
| Glutamate | ↑ | Brain | iNOS expression |
| Glutamine | ↑ | Macrophages | iNOS expression |
| Glutamine | ↓ | Intestine | iNOS expression |
| High-fat diet | ↑ | Islets, liver & colon | iNOS activity |
| High-salt diet | ↓ | EC & kidney | iNOS expression |
| Iron | ↑ | Macrophages & kidney | iNOS expression |
| Iron | ↓ | EC | iNOS expression |
| LDL (oxidized) | ↑ | Macrophages | iNOS activity |
| Lead | ↓ | Macrophages | iNOS expression |
| Linoleic acid | ↑ | Macrophages | iNOS expression |
| Lysine | ↓ | Many cell types | Arginine transport |
| Melatonin | ↓ | Neuronal cells | iNOS & BH4 |
| Niacin | ↓ | Lung | iNOS expression |
| Nickel | ↑ | Macrophages | iNOS expression |
| Phytanic acid | ↑ | VSMC | iNOS expression |
| Phytoestrogens | ↓ | Tumor cells | iNOS expression |
| Polyphenols | ↓ | Macrophages & tumors | iNOS expression |
| Polyphenols | ↑ | Arteries | iNOS expression |
| Protein deficiency | ↓ | Macrophages and others | iNOS activity |
| Taurine | ↓ | Many cell types | iNOS expression |
| Vitamin A | ↑ | Macrophages | iNOS expression |
| Vitamin A | ↓ | EC, VSMC & myocytes | iNOS expression |
| Vitamin B6 | ↓ | Colon | iNOS expression |
| Vitamin D3 | ↑ | Macrophages | iNOS expression |
| Vitamin D3 | ↓ | Neuronal cells | iNOS expression |
| Vitamin D3 | ↓ | VSMC | iNOS expression |
| Vitamin E | ↓ | EC, VSMC & macrophages | iNOS expression |

CLA, conjugated linoleic acid; GI, gastrointestinal tissues. ↑, increase; ↓, decrease.

As a major vasodilator, a mediator of immune function, a neurotransmitter, a cytotoxic free radical (at high levels), and a signaling molecule, NO plays crucial roles in virtually every cellular and organ function in the body. A deficiency of NO results in abnormalities in nervous, muscular, circulatory, respiratory, digestive, urinary, reproductive, endocrine, and immune systems. In contrast, excessive production of NO is destructive to cells and may mediate the pathogenesis of autoimmune diseases, allograft rejection, and septic shock. Dietary factors are either beneficial to health or contribute to the pathogenesis of chronic diseases partially through modulation of NO production (1-4). As the physiological precursor of NO and a potent regulator of intracellular concentrations of cofactors for NOS, L-arginine provides an effective nutritional treatment for a wide array of disorders (Table 3). Remarkably, physiological levels of NO increase the oxidation of energy substrates (e.g., fatty acids and glucose) and reduce fat deposition in an animal model of type-II diabetes mellitus (5). Dietary arginine supplementation may provide a promising solution to ameliorate the current global obesity epidemic.

Table 3. The role of NO in mediating the beneficial effects of arginine on the body

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|---|--|
| Hormone secretion | Insulin, glucagons, growth hormone, prolactin, placental lactogen |
| Reproduction | Spermatogenesis, male fertility, ovulation, ovarian steroidogenesis, embryo implantation, fetal growth, placental angiogenesis, placental growth, erectile dysfunction, preeclampsia, uterine contractility, preterm labor |
| Endothelial dysfunction in patients with CVRF | Hypercholesterolemia, smoking, hypertension, diabetes, obesity, insulin resistance, aging |
| Cardiovascular disorders | Coronary and peripheral arterial diseases, ischemia/reperfusion injury, heart failure and stroke, sickle cell anemia, renal disease with systemic hypertension |
| Immune function | T-cell proliferation, B-cell maturation, antibody production by B-cells, killing of pathogens |
| Digestive disorders | Gastrointestinal and liver injury, necrotizing enterocolitis, intestinal integrity |
| Tumor growth | Inhibition of tumorigenesis at early stage |
| Cell signaling and metabolism | Nutrient metabolism, fat and glucose oxidation, insulin sensitivity |
| Tissue repair, remodeling and function | Wound healing, angiogenesis, skeletal muscle and brain function |

CVRF, cardiovascular risk factors.

In conclusion, NO displays enormous versatility and importance in cell metabolism, nutrition, and function. The discovery of NO synthesis in mammalian cells has unified the diverse areas of life science research, including nutrition, immunology, physiology, and health. The regulation of NO generation from arginine by dietary factors (including macro- and micronutrients as well as phytochemicals) has been, and will continue to be, a rich area of biomedical research. New knowledge about nutritional regulation of NO synthesis is very beneficial for improving health and preventing disease in both humans and animals.

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