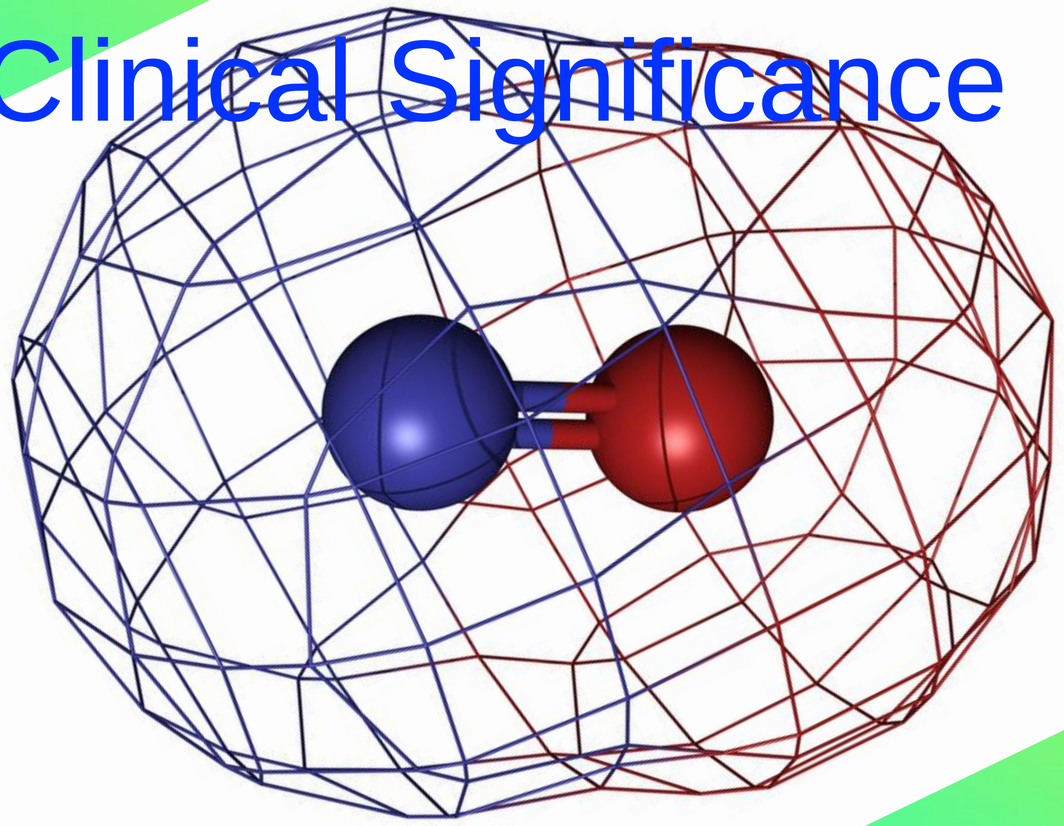
Nitric Oxide: The Ins and Outs of Its Clinical Significance

Christopher Bump, DC, MS, IFMCP, CNS

Nitric Oxide: The Ins and Outs of Its Clinical Significance



Dr. Christopher Bump
Integrated Health Symposium
February 2024
drcjbump@gmail.com

*NO - Notable Facts

- Up until 1987 *NO was known to be ONLY a toxic pollutant
- Robert Furchgott, Louis Ignarro and Ferid Murad's discovery created an entirely new paradigm regarding nature: that a molecule could be both a toxicant and a bioactive essential molecule.
- *NO is highly unique: it is small, it is uncharged, it has an unpaired electron and it is a gas.

***N=O**

7 8

Nitric Oxide

Signs and Symptoms of Low *NO

- Hypertension
- CV Disease
- Gastrointestinal distress
- Myalgia, paresthesia
- Low Stamina
- Cyanosis
- Numbness, chest pain, swelling, bulging veins
- History of NSAID use
- Erectile dysfunction
- Imbalanced hormones
- Brain fog

References for slide #3

1. Lee J. Nitric oxide in the kidney : its physiological role and pathophysiological implications. Electrolyte Blood Press. 2008;6(1):27-34. doi:10.5049/EBP.2008.6.1.27.
2. Paul V, Ekambaram P. Involvement of nitric oxide in learning & memory processes. Indian J Med Res. 2011 May;133(5):471-8. PMID: 21623030; PMCID: PMC3121276.
3. Dhir A, Kulkarni SK. Nitric oxide and major depression. Nitric Oxide. 2011 Apr 30;24(3):125-31. doi: 10.1016/j.niox.2011.02.002. Epub 2011 Feb 16. PMID: 21335097.
4. Burnett AL. The role of nitric oxide in erectile dysfunction: implications for medical therapy. J Clin Hypertens (Greenwich). 2006;8(12 Suppl 4):53-62. doi:10.1111/j.1524-6175.2006.06026.x.
5. Sohail R, Mathew M, Patel KK, et al. Effects of Non-steroidal Anti-inflammatory Drugs (NSAIDs) and Gastroprotective NSAIDs on the Gastrointestinal Tract: A Narrative Review. Cureus. 2023;15(4):e37080. Published 2023 Apr 3. doi:10.7759/cureus.37080.
6. Dyakova EY, Kapilevich LV, Shylko VG, Popov SV, Anfinogenova Y. Physical exercise associated with NO production: signaling pathways and significance in health and disease. Front Cell Dev Biol. 2015;3:19. Published 2015 Apr 2. doi:10.3389/fcell.2015.00019.
7. Sverdlov AL, Ngo DT, Chan WP, Chirkov YY, Horowitz JD. Aging of the nitric oxide system: are we as old as our NO?. J Am Heart Assoc. 2014;3(4):e000973. Published 2014 Aug 18. doi:10.1161/JAHA.114.000973.
8. Picón-Pagès P, Garcia-Buendia J, Muñoz FJ. Functions and dysfunctions of nitric oxide in brain. Biochim Biophys Acta Mol Basis Dis. 2019 Aug 1;1865(8):1949-1967. doi: 10.1016/j.bbadis.2018.11.007. Epub 2018 Nov 27. PMID: 30500433.
9. Tripathi P. Nitric oxide and immune response. Indian J Biochem Biophys. 2007 Oct;44(5):310-9. PMID: 18341206.
10. Félétou M. The Endothelium: Part 1: Multiple Functions of the Endothelial Cells—Focus on Endothelium-Derived Vasoactive Mediators. San Rafael (CA): Morgan & Claypool Life Sciences; 2011. Available from: https://www.ncbi.nlm.nih.gov/books/NBK57149/.
11. Luo Y, Zhu Y, Basang W, Wang X, Li C, Zhou X. Roles of Nitric Oxide in the Regulation of Reproduction: A Review. Front Endocrinol (Lausanne). 2021;12:752410. Published 2021 Nov 19. doi:10.3389/fendo.2021.752410.
12. Malone-Povolny MJ, Maloney SE, Schoenfisch MH. Nitric Oxide Therapy for Diabetic Wound Healing. Adv Healthc Mater. 2019;8(12):e1801210. doi:10.1002/adhm.201801210.
13. Tsukiyama Y, Ito T, Nagaoka K, Eguchi E, Ogino K. Effects of exercise training on nitric oxide, blood pressure and antioxidant enzymes. J Clin Biochem Nutr. 2017;60(3):180-186. doi:10.3164/jcbn.16-108.
14. Kobayashi J, Ohtake K, Uchida H. NO-Rich Diet for Lifestyle-Related Diseases. Nutrients. 2015;7(6):4911-4937. Published 2015 Jun 17. doi:10.3390/nu7064911.

Published in final edited form as:
Circ Res. 2020 January 03; 126(1): 129–158. doi:10.1161/CIRCRESAHA.119.315626.

Role of Nitric Oxide Carried by Hemoglobin in Cardiovascular Physiology: Developments on a Three-Gas Respiratory Cycle

Richard T. Premont[1,2], **James D. Reynolds**[1,2,3], **Rongli Zhang**[1,4], **Jonathan S. Stamler**[1,2,4]

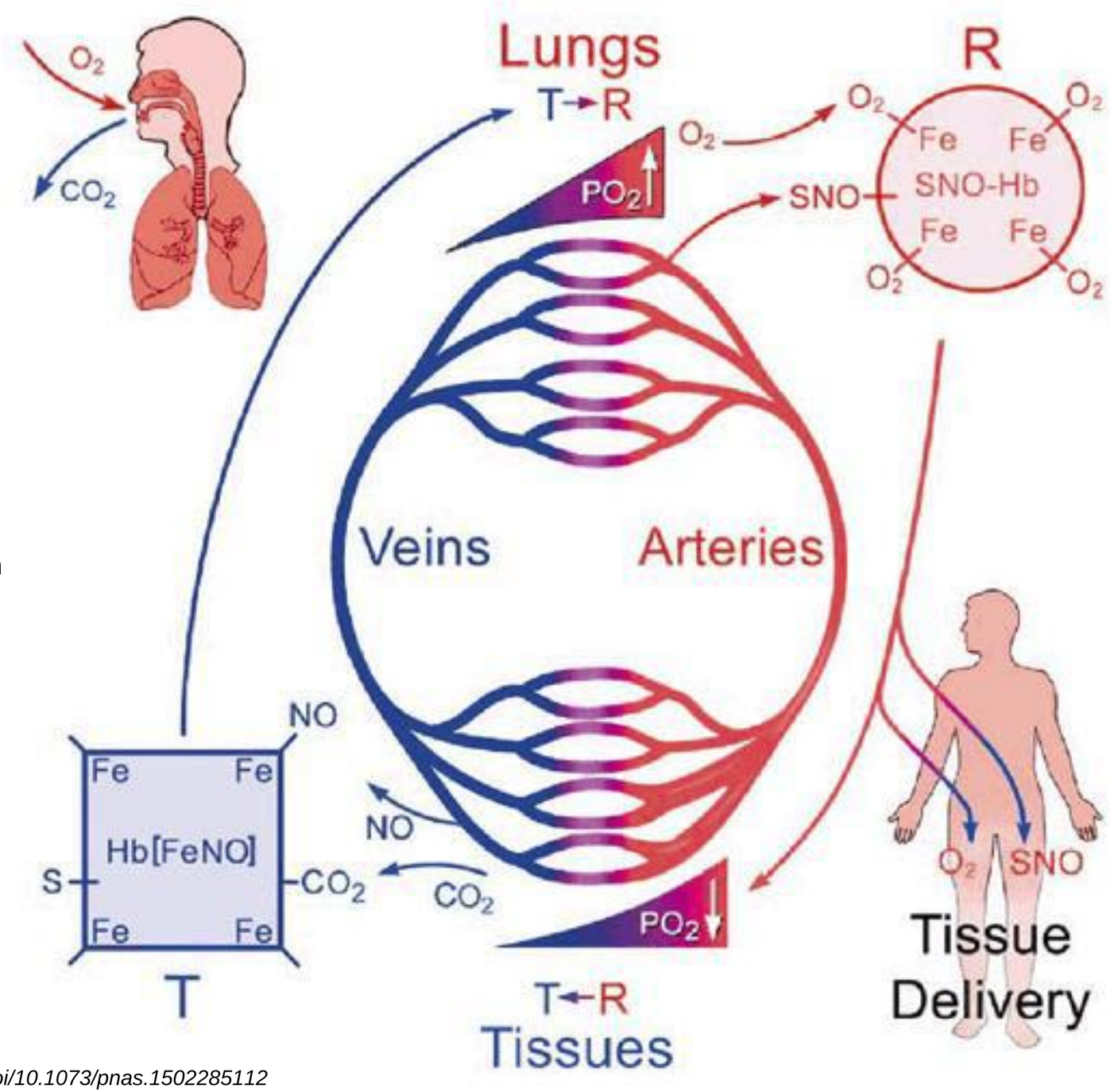
[1]Institute for Transformative Molecular Medicine, Case Western Reserve University School of Medicine, Cleveland, Ohio

Abstract

A continuous supply of oxygen is essential for the survival of multi-cellular organisms. The

A continuous supply of oxygen is essential for the survival of multi-cellular organisms. The understanding of how this supply is regulated in the micro-vasculature has evolved from viewing erythrocytes (red blood cells, RBCs) as passive carriers of oxygen to recognizing the complex interplay between hemoglobin and oxygen, carbon dioxide, and nitric oxide – the three-gas respiratory cycle – that insures adequate oxygen and nutrient delivery to meet local metabolic demand. In this context, it is blood flow not blood oxygen content that is the main driver of tissue oxygenation by RBCs.

Blood flow to tissues is actually more important in most circumstances than how much oxygen is carried by hemoglobin. The respiratory cycle is actually a three-gas system.



www.pnas.org/cgi/doi/10.1073/pnas.1502285112

Nitric Oxide 129 (2022) 25–29

Nitric oxide bioavailability for red blood cell deformability in the microcirculation: A review of recent progress

Jun Kobayashi [a,*], Kazuo Ohtake [b], Isamu Murata [c], Kunihiro Sonoda [d]

[a] Department of Clinical Dietetics and Human Nutrition, Faculty of Pharmacy and Pharmaceutical Science, Josai University, Saitama, Japan
[b] Division of Physiology, School of Pharmaceutical Sciences, Faculty of Pharmacy and Pharmaceutical Science, Josai University, Saitama, Japan
[c] Laboratory of Pharmacotherapeutics and Neuropsychopharmacology, Faculty of Pharmaceutical Science, Josai University, Saitama, Japan
[d] Department of Food and Nutritional Environment, College of Human Life and Environment, Kinjo Gakuin University, Nagoya, Japan

ARTICLE INFO

Keywords:
Nitric oxide
Nitrite

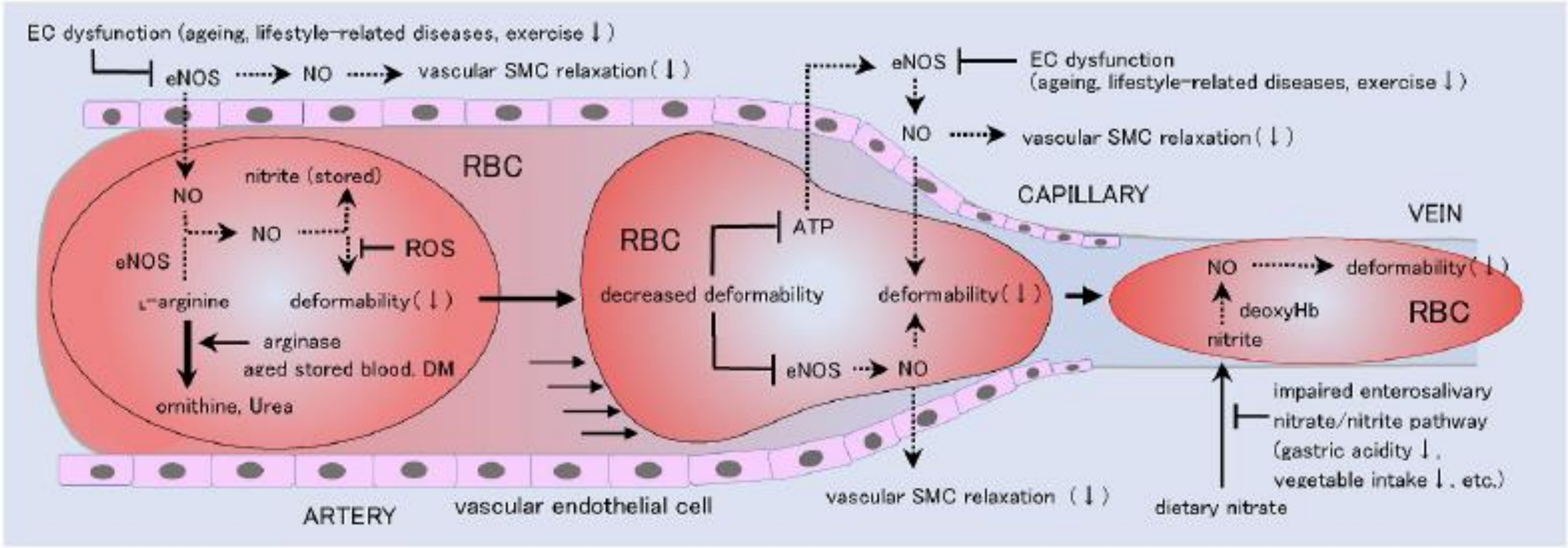
ABSTRACT

The rheological properties of red blood cells (RBCs) play an important role in their microcirculation. RBCs can elastically deform in response to mechanical forces to pass through narrow vessels for effective gas exchange in

However, endogenously, and exogenously generated NO protects RBC membrane flexibility from further oxidative modification by shielding redox-sensitive cysteine residues with a glutathione cap. Recent studies have shown that nitrate-rich diets and moderate exercise can enhance NO production to increase RBC deformability by increasing the interplay between RBCs and vascular endothelium-mediated NO bioavailability for microcirculation.

with vascular endothelial dysfunction.

Proposed molecular mechanism of decrease in RBC deformability following impaired NO generation and its bioavailability



Nitric Oxide 129 (2022) 25–29

Cell
Leading Edge

CellPress
OPEN ACCESS

Review

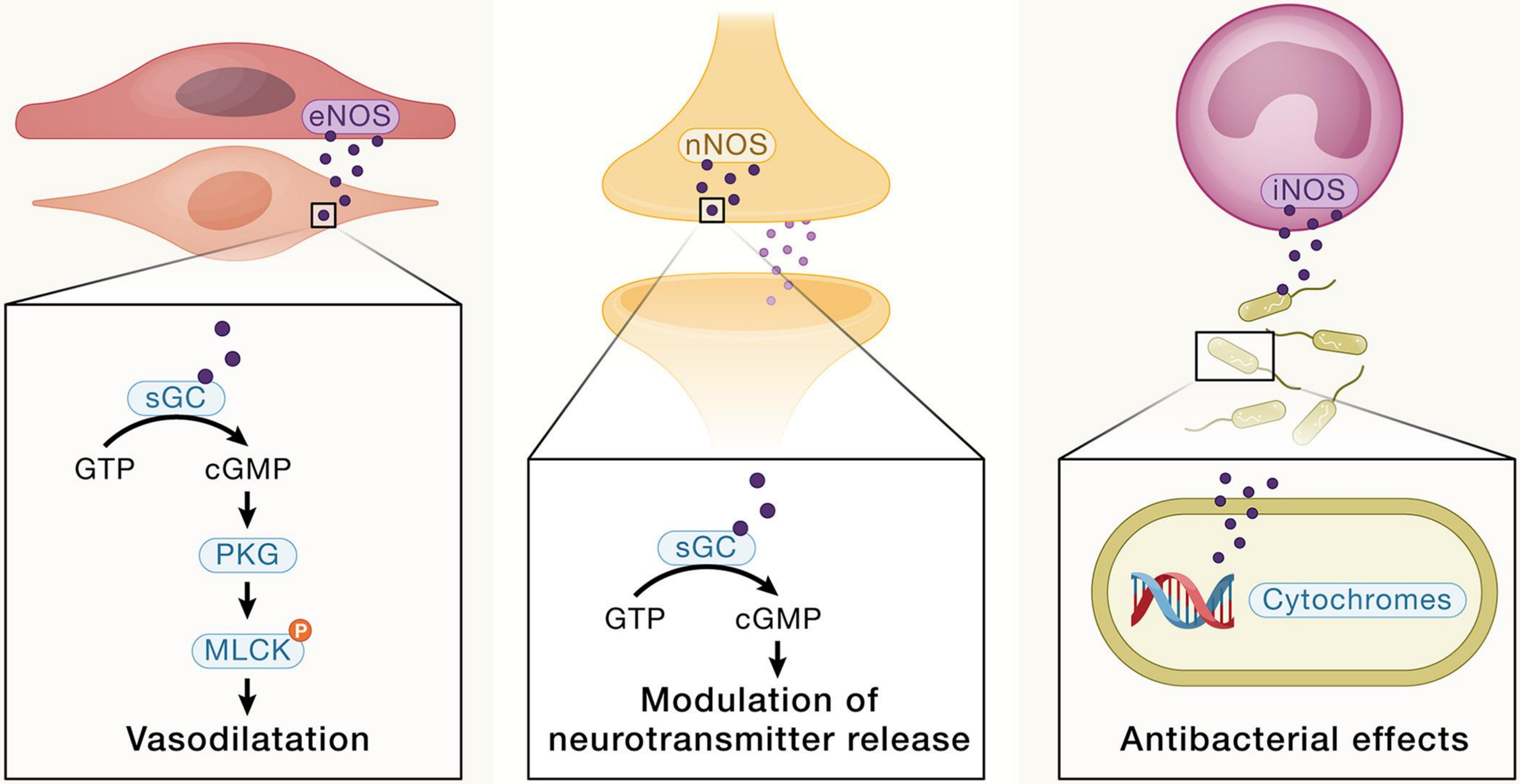
Nitric oxide signaling in health and disease

Jon O. Lundberg[1,*] and Eddie Weitzberg[1,*]
[1]Department of Physiology and Pharmacology, Karolinska Institutet, Stockholm, Sweden
*Correspondence: jon.lundberg@ki.se (J.O.L.), eddie.weitzberg@ki.se (E.W.)
https://doi.org/10.1016/j.cell.2022.06.010

SUMMARY

The surprising discovery that the diatomic gas nitric oxide (NO) is generated by mammalian cells and serves to regulate a multitude of physiological processes has continued to fascinate biologists for almost four de-

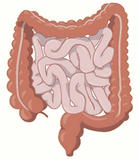
The biochemistry of NO is complex and novel insights into the control of NO biosynthesis and mechanisms of signal transduction are continuously emerging. NO is a key regulator of cardiovascular function, metabolism, neurotransmission, immunity, and more, and aberrant NO signaling is a central feature of many major disorders including cardiovascular disease, diabetes, and cancer.



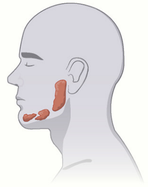
Lundber JO., Weitzberg E. Nitric oxide signaling in health and disease. Cell 185, August 4, 2022

The nitrate-nitrite-nitric oxide pathway

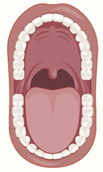
Dietary nitrate is obtained mainly from green leafy vegetables



Nitrate is absorbed in the upper GI tract and mixes in blood with endogenous nitrate from NO synthases

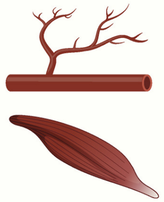


Nitrate is actively taken up from blood by the salivary glands and accumulates in saliva



In the oral cavity commensal bacteria reduce nitrate to the more reactive nitrite anion

Parts of the nitrite is reduced to NO and other bioactive nitrogen oxides in the acidic stomach



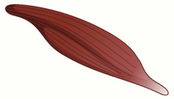
Nitrite entering the circulation can be reduced to NO in blood and tissues via various enzymatic and non-enzymatic pathways

Effects of dietary nitrate

Brain

Increased perfusion in frontal lobe white matter

Skeletal muscle



Enhanced contraction

Increased muscle blood flow

Mitochondria

Improved efficiency (P/O ratio)

Reduced proton leak

Blood

Reduced platelet aggregation ex vivo

Vasculature

Decreased blood pressure

Increased flow mediated dilation

Preservation of endothelial function

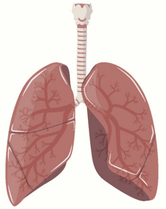
Improved vascular compliance

Bone marrow

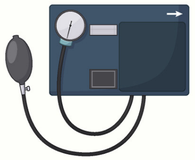
Mobilization of circulating angiogenic cells

Proposed clinical targets

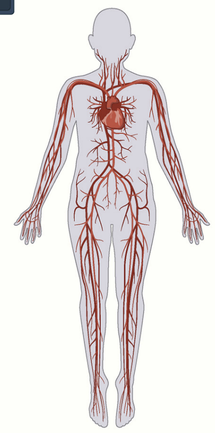
Exercise performance



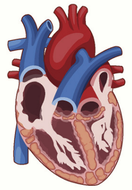
Pulmonary hypertension COPD



Hypertension



Peripheral artery disease



Heart failure

Lundber JO., Weitzberg E. Nitric oxide signaling in health and disease. Cell 185, August 4, 2022

Clinical Effects of *NO

- Hypertension
- Erectile dysfunction…both male and female
- Vascular dementia - Alzheimers
- Diabetes
- Small vessel disease
- Wound healing including anti-biofilm
- Anticancer effects
- Pulmonary hypertension
- Cognition
- Ischemia and reperfusion injury
- Gastric mucosa protection
- Anti-thrombotic
- Improved cognition
- Improved athletic performance
- Glucose regulation
- Anti-microbial
- Anti-inflammatory

Cell Metabolism
Review

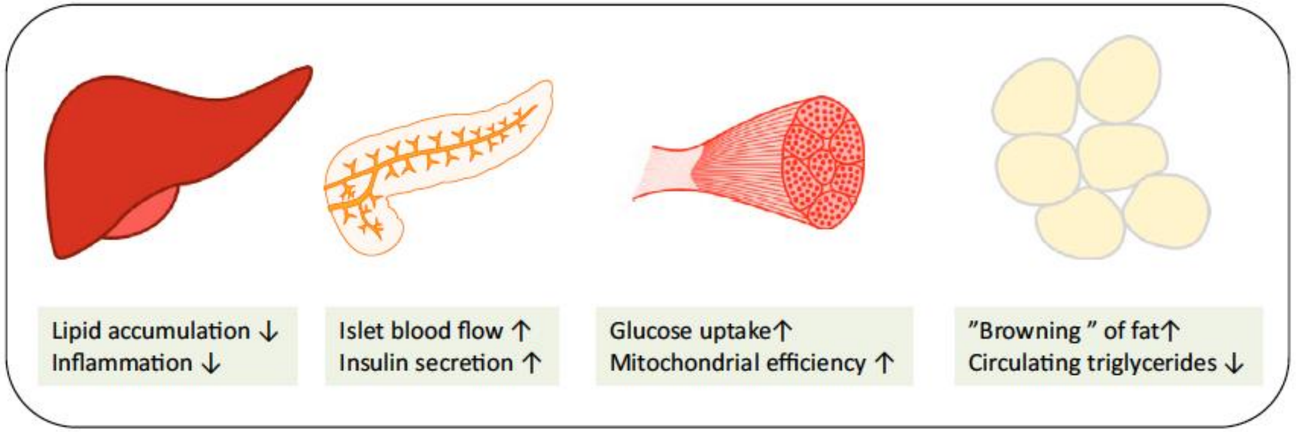
Metabolic Effects of Dietary Nitrate in Health and Disease

Jon O. Lundberg,[1,*] Mattias Carlström,[1,*] and Eddie Weitzberg[1,*]
[1]Department of Physiology and Pharmacology, Karolinska Institutet, 171 77 Stockholm, Sweden
*Correspondence: jon.lundberg@ki.se (J.O.L.), mattias.carlstrom@ki.se (M.C.), eddie.weitzberg@ki.se (E.W.)
https://doi.org/10.1016/j.cmet.2018.06.007

The described cardio-metabolic effects of dietary nitrate from experimental and clinical studies include lowering of blood pressure, improved endothelial function, increased exercise performance, and reversal of metabolic syndrome, as well as anti-diabetic effects. The mechanisms underlying the salutary metabolic effects of nitrate are being revealed and include interaction with mitochondrial respiration, activation of key metabolic regulatory pathways, and reduction of oxidative stress.

in health and disease.

Examples of How Dietary Nitrate Affects Metabolic Functions in the Liver, Pancreas, Skeletal Muscle, and AdiposeTissue



- Decreased lipid accumulation
- Decrease inflammation
- Increase pancreatic islet blood flow
- Increase insulin secretion
- Increase glucose uptake
- Increase Mitochondrial efficiency
- Increased “Browning” of fat
- Decrease circulating triglycerides

Cell Metabolism 28, July 3, 2018

Curr Cardiol Rep (2017) 19: 87
DOI 10.1007/s11886-017-0898-y

PSYCHOLOGICAL ASPECTS OF CARDIOVASCULAR DISEASES (A STEPTOE, SECTION EDITOR)

Cardiovascular Disease, the Nitric Oxide Pathway and Risk of Cognitive Impairment and Dementia

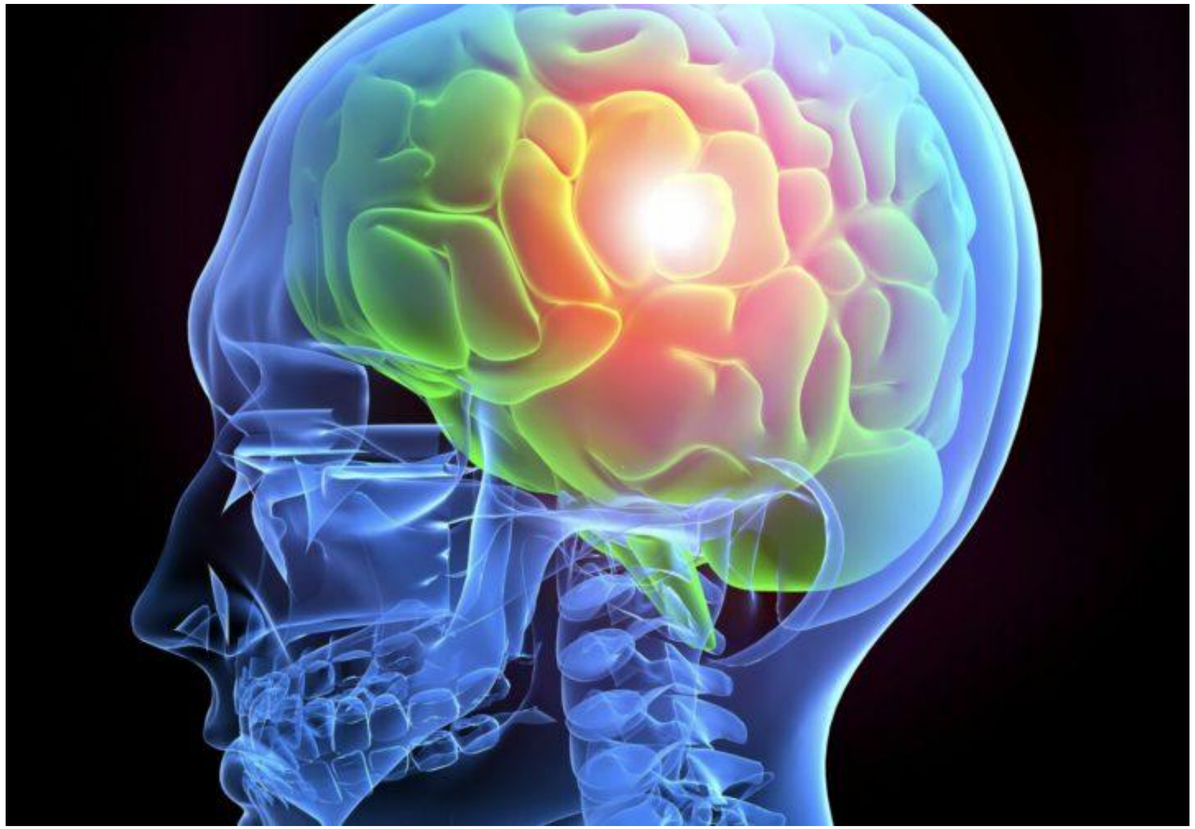
Blossom C. M. Stephan[1] · Stephanie L. Harrison[2] · Hannah A. D. Keage[3] · Abrar Babateen[4,5] · Louise Robinson[1] · Mario Siervo[4]

Evidence from epidemiological studies suggests that the presence of CVD and its risk factors in midlife is associated with an increased risk of later life cognitive impairment and dementia. It is unclear what is driving this association, but risk may be conveyed via an increase in neurodegeneration (e.g. amyloid deposition), vascular å (e.g. small vessel disease) and mechanistically due to increased levels of oxidative stress and inflammation as well as changes in NO bioavailability.

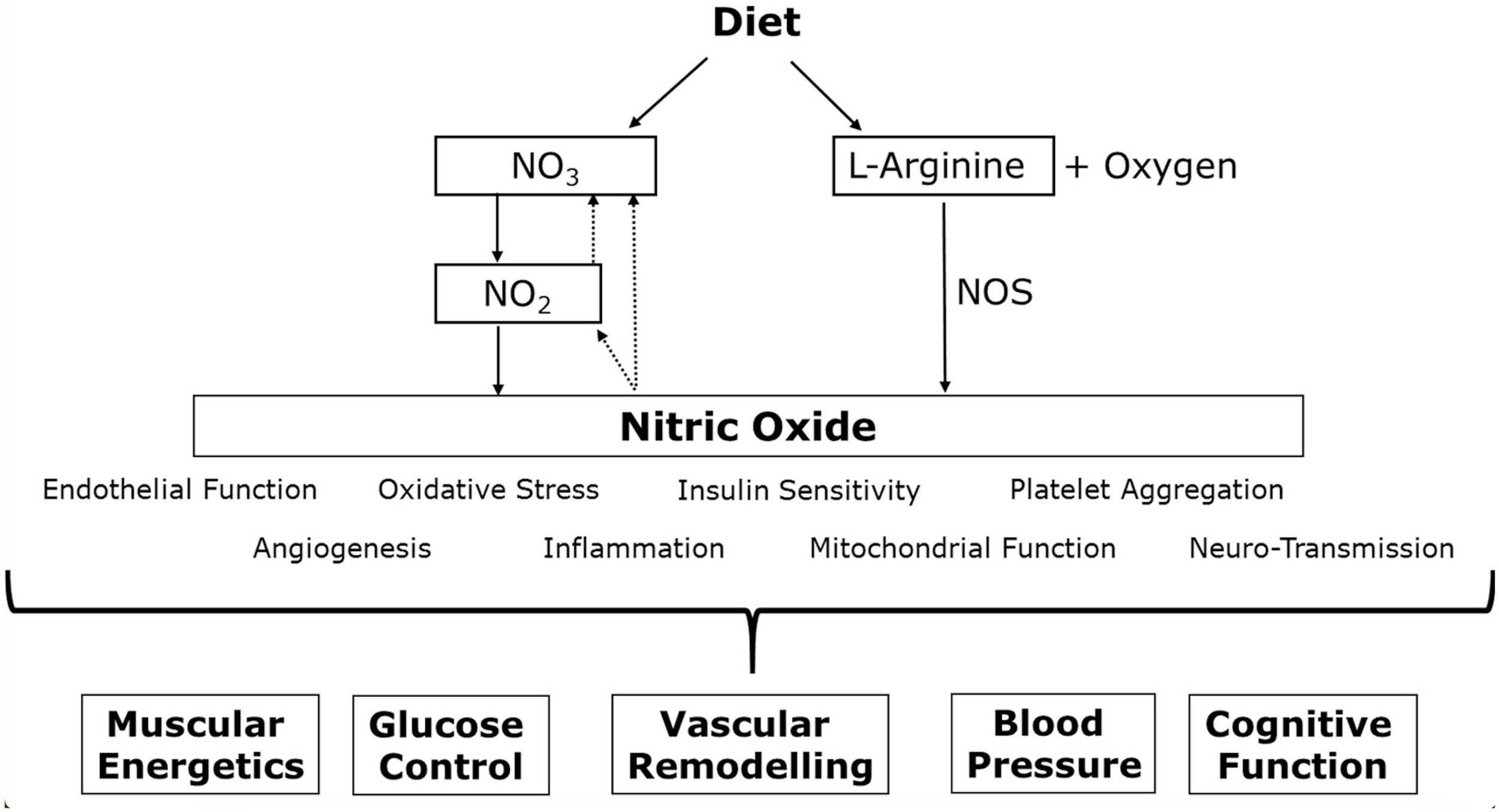
associated with an increased risk of later life cognitive impair-

Increased Risk Factors for Cognitive Decline and Dementia

- Chronic inflammation
- Increased oxidative stress
- Reduce vascular supply
- Alterations of Blood Brain Barrier
- Decreased Nitric Oxide



Curr Cardiol Rep (2017) 19: 87 DOI 10.1007/s11886-017-0898-y



Curr Cardiol Rep (2017) 19: 87 DOI 10.1007/s11886-017-0898-y

Stroke

FOCUSED UPDATES

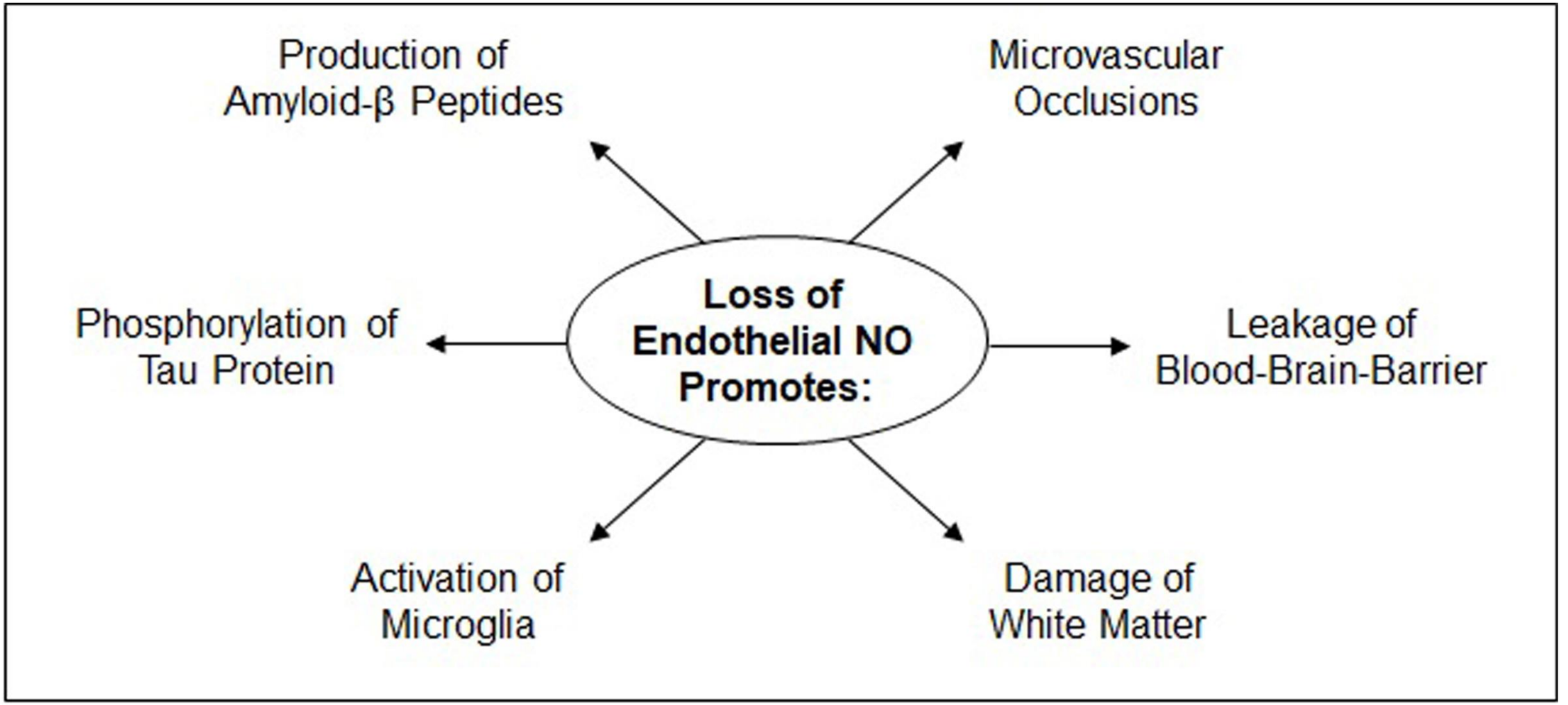
Emerging Roles of Endothelial Nitric Oxide in Preservation of Cognitive Health

Zvonimir S. Katusic, MD, PhD; Livius V. d'Uscio, PhD; Tongrong He, MD, PhD

Zvonimir S. Katusic. Stroke. Emerging Roles of Endothelial Nitric Oxide in Preservation of Cognitive Health, Volume: 54, Issue: 3, Pages: 686-696, DOI: (10.1161/STROKEAHA.122.041444)

ABSTRACT: eNOS (endothelial nitric oxide synthase) is critically important enzyme responsible for regulation of cardiovascular homeostasis. Under physiological conditions, constitutive eNOS activity and production of endothelial nitric oxide (NO) exert

Prior studies established that loss of neuroprotective function of endothelium significantly contributes to vulnerability of brain to neurodegeneration and dementia. More precisely, impaired eNOS (endothelial nitric oxide synthase)/nitric oxide (NO) signaling seems to be an essential molecular mechanism linking cardiovascular risk factors with altered brain function and development of cognitive impairment.



Detrimental effects of endothelial nitric oxide (NO) deficiency contributing to impairment of cognitive function. Exact longitudinal sequence of described functional alterations remain to be determined.

Zvonimir S. Katusic. Stroke. Emerging Roles of Endothelial Nitric Oxide in Preservation of Cognitive Health, Volume: 54, Issue: 3, Pages: 686-696, DOI: (10.1161/STROKEAHA.122.041444)

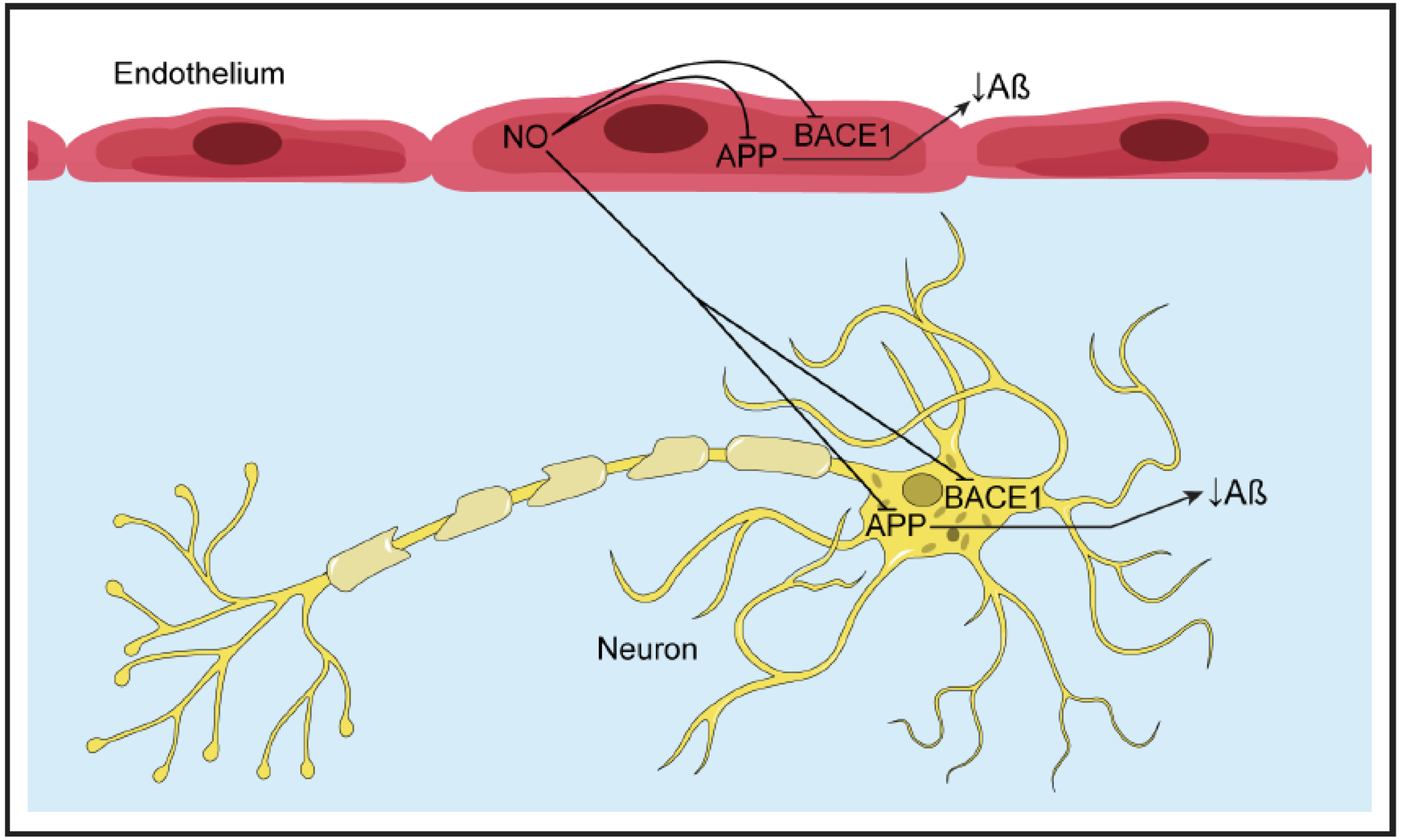


Figure 2. Schematic representation of the inhibitory effects of endothelial nitric oxide (NO) on expression of APP (amyloid precursor protein) and BACE1 (β-site APP-cleaving enzyme 1), and production of Aβ (amyloid-β) in endothelial and neuronal cells.

Mol. Nutr. Food Res. 2016, *60*, 185–202 DOI 10.1002/mnfr.201500313

REVIEW

A 'green' diet-based approach to cardiovascular health? Is inorganic nitrate the answer?

Krishnaraj Sinhji Rathod, Shanti Velmurugan* and Amrita Ahluwalia*

William Harvey Research Institute, Barts NIHR Cardiovascular Biomedical Research Unit, Barts & The London Medical School, Queen Mary University of London, Charterhouse Square, London, UK

Ingestion of fruit and vegetables rich in inorganic nitrate (NO_3^-) has emerged as an effective method for acutely elevating vascular nitric oxide (NO) levels through formation of an NO_2^- intermediate. As such a number of beneficial effects of NO_3^- and NO_2^- ingestion have been demonstrated including reductions in blood pressure, measures of arterial stiffness and platelet activity. The pathway for NO generation from such dietary interventions involves the activity of facultative oral microflora that facilitate the reduction of inorganic NO_3^-, ingested in the

Received: April 21, 2015
Revised: June 16, 2015
Accepted: July 10, 2015

Ingestion of fruit and vegetables rich in inorganic nitrate (NO3 −) has emerged as an effective method for acutely elevating vascular nitric oxide (NO) levels through formation of an NO2−intermediate. As such a number of beneficial effects of NO3 − and NO2 − ingestion have been demonstrated including reductions in blood pressure, measures of arterial stiffness and platelet activity.

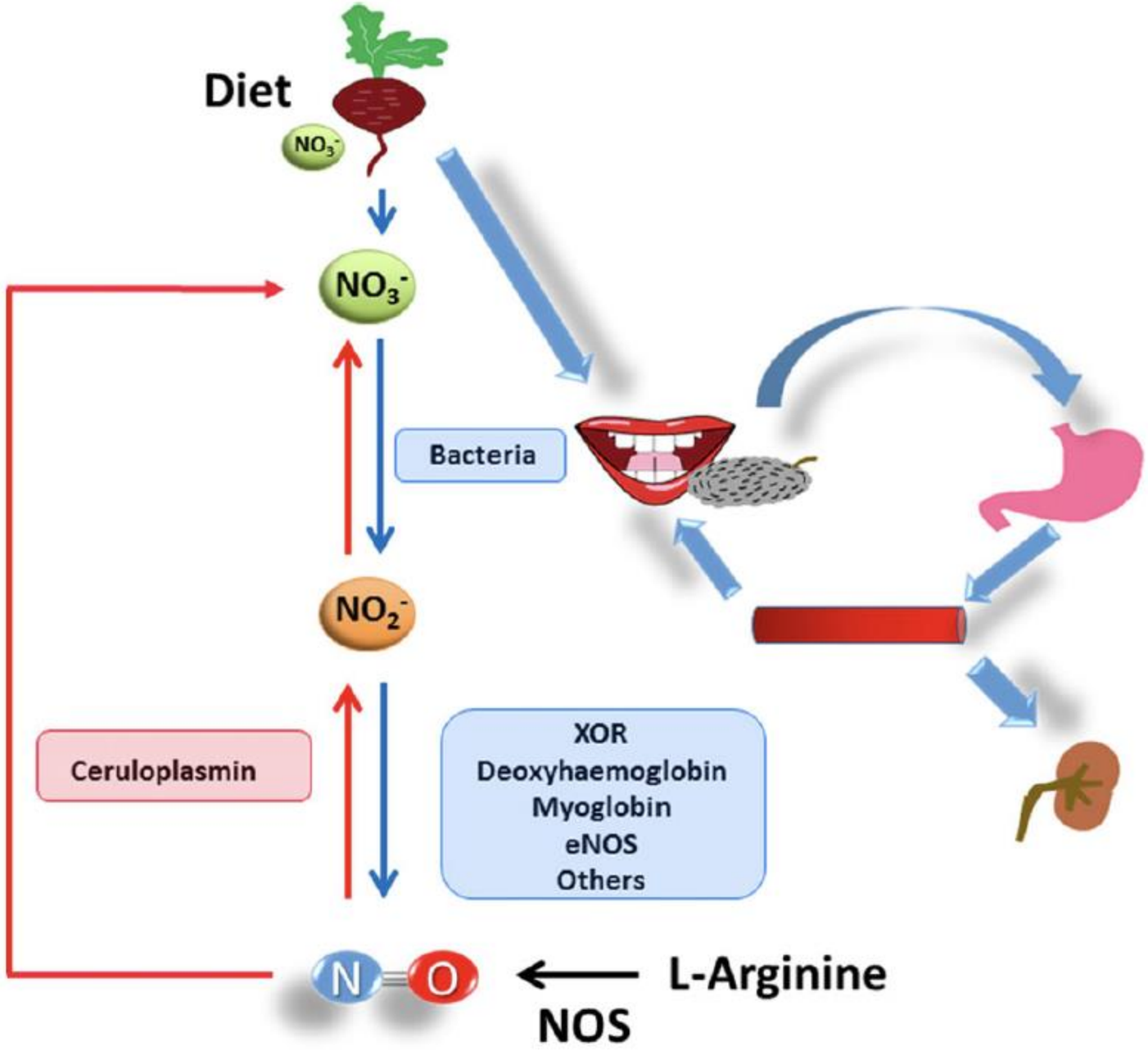


Figure 2. Pathways for endogenous NO generation: The L-arginine:NO synthase pathway, the nitrate–nitrite pathway of NO generation and the enterosalivary circulation. In health circulating NO_3^- and NO_2^- levels are derived from two distinct sources. These are from the diet through a sequential in vivo process of chemical reduction and secondly from the oxidation of NO generated from the constitutively active conventional pathway involving L-arginine and NO synthase (NOS).

Clinical potential of NO therapy for CV Health

- Reduced blood pressure
- Improved flow mediated dilatation (FMD)
- Reduced ox LDL
- Improved platelet reactivity…less cell wall adhesion
- Reduced damaging effect of cardiac IR injury. (Ischemia-reperfusion)
- Reduced pulmonary hypertension

Zvonimir S. Katusic. Stroke, Volume: 54, Issue: 3, Pages: 686-696, DOI: (10.1161/STROKEAHA.122.041444)

Ren et al. Cardiovasc Diabetol (2017) 16:52
DOI 10.1186/s12933-017-0531-9

Cardiovascular Diabetology

ORIGINAL INVESTIGATION

Open Access

Advanced glycation end-products decreases expression of endothelial nitric oxide synthase through oxidative stress in human coronary artery endothelial cells

Xiaomei Ren[1], Liqun Ren[1], Qin Wei[2*], Hua Shao[3], Long Chen[2] and Naifeng Liu[4]

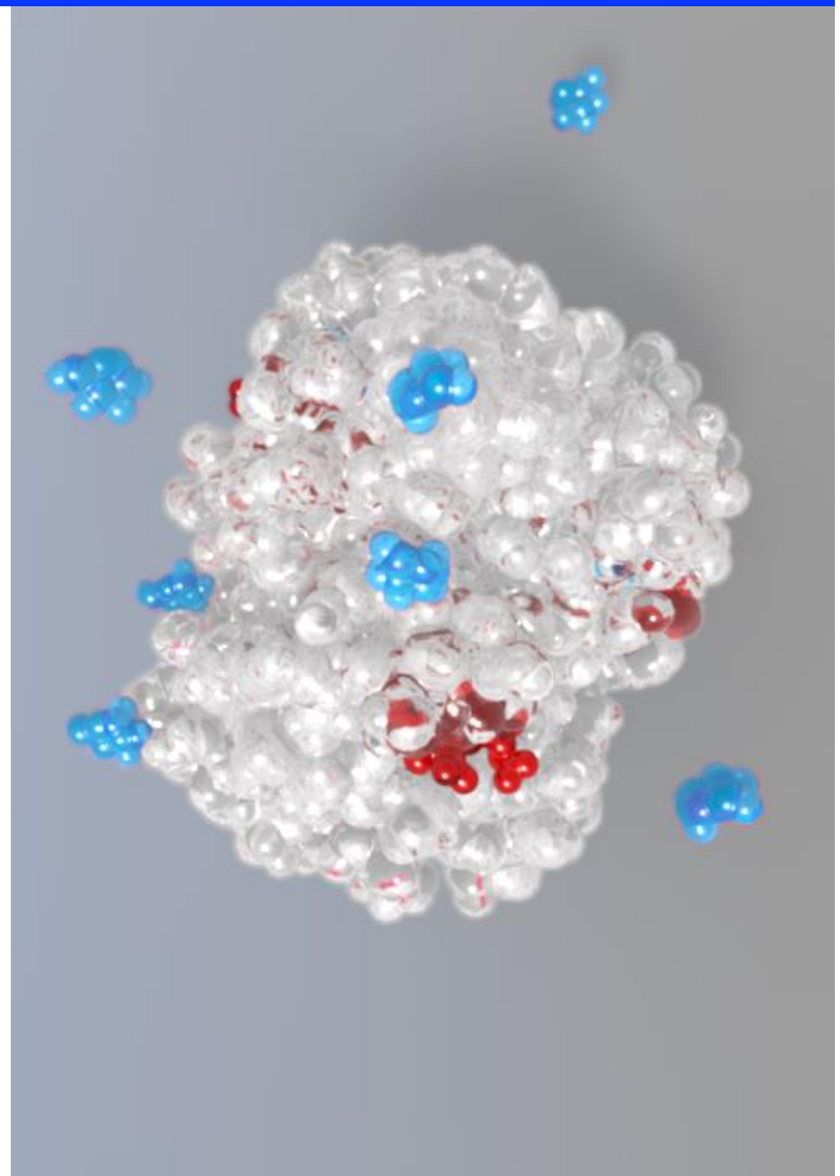
Abstract

AGE-p was inversely associated with FMD in diabetic patients with coronary artery atherosclerosis in our study. After treated with AGEs, HCAECs showed significant reductions of eNOS mRNA and protein levels including eNOS, eNOS enzyme activity, and cellular nitric oxide (NO) levels, whereas superoxide anion production was significantly increased. In addition, AGEs significantly decreased mitochondrial membrane potential, ATP content and catalase and superoxide dismutase (SOD) activities, whereas it increased NADPH oxidase activity.

and mechanisms of AGEs on endothelial dysfunction in HCAECs.

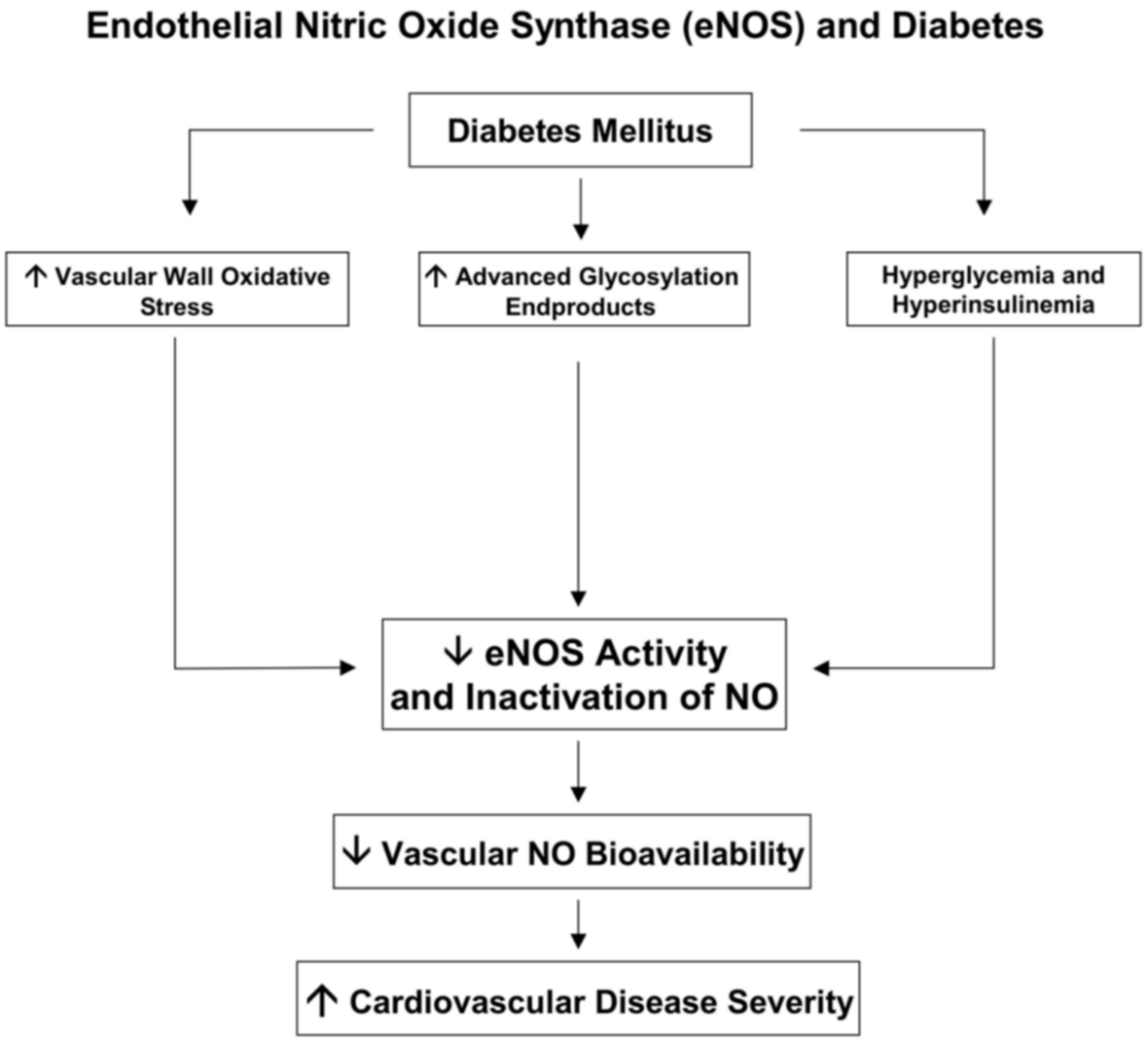
Advanced Glycation End Products and *NO

- Increased AGEs = Decreased flow mediated dilation. (FMD)
- Decreased eNOS production
- Reduced eNOS enzyme activity
- Decreased cellular *NO levels
- Significantly reduced mitochondrial membrane potential, ATP content and antioxidant activity.
- Increased oxidative damage



Rogers et al Clin Transplant. 2004;18 Suppl 12:7-11

Diabetes Leads to Insufficient N.O. Production

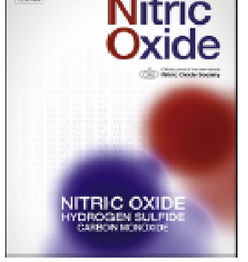


Rogers et al Clin Transplant. 2004;18 Suppl 12:7-11

Contents lists available at ScienceDirect

Nitric Oxide

journal homepage: www.elsevier.com/locate/yniox



Anti-obesity and anti-diabetic effects of nitrate and nitrite

Asghar Ghasemi*, Sajad Jeddi

Endocrine Physiology Research Center, Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran

ARTICLE INFO

Article history:
Received 27 April 2017
Received in revised form
2 July 2017

ABSTRACT

Prevalence of obesity is increasing worldwide and type 2 diabetes to date is the most devastating complication of obesity. Decreased nitric oxide bioavailability is a feature of obesity and diabetes that links these two pathologies. Nitric oxide is synthesized both by nitric oxide synthase enzymes from L-arginine and nitric oxide synthase-independent from nitrate/nitrite. Nitric oxide production from nitrate/

on, all effects that are potentially promising for management of obesity and diabetes. Based on

Effect of Nitrate/Nitrite On Metabolic Markers and Glucose Tolerance

- *Decreased fasting glucose*
- *Decreased fasting insulin*
- *Improved glucose tolerance*
- *Decrease HbA1C*

Table 1
Effect of nitrate/nitrite administration on metabolic markers and glucose tolerance in animal models of type 2 diabetes and metabolic syndrome.

Study	Animal	Study duration (weeks)	Dose of nitrate/nitrite in drinking water	Fasting glucose	Fasting insulin	Glucose tolerance[a]	HbA1c	HOMA-IR
[21]	eNOS$^{-/-}$ mice (a model of metabolic syndrome)	10	85 mg/L $NaNO_3$	↓	↓	↑	↓	NR
[13]	Type 2 diabetic db/db mice	4	50 mg/L NO_2	↓	NR	NR	NR	NR
[144]	Type 2 diabetic Wistar rats	8	100 mg/L NaNO3	↓	NR	↑	NR	NR
[19]	Type 2 diabetic KKA^{y} mice	10	50 and 150 mg/L NO_2	↓	↓	↑ (only in 150 mg/L)	NR	↓
[150]	Sprauge-Dawley rats (fructose-fed model of metabolic syndrome)	6	150 mg/kg NaNO3 gavage once daily	↔	↔	NR	NR	↓
[151]	Wistar rats	17	550 mg/L NaNO3	↑	↓	NR	↑	NR
[145]	Old obese ZSF1 rats (a model of metabolic syndrome)	14	50 and 100 mg/L $NaNO_2$	↓	↔	↑	↓	NR
[152]	Obese type 2 diabetic Wistar rats	8	50 mg/L $NaNO_2$	↓	↓	↑	↔	NR

HOMA-IR, homeostasis model of insulin resistance; HbA1c, glycated hemoglobin; NR, Not reported.
[a] Assessed by intraperitoneal glucose tolerance test.

A. Ghasemi, S. Jeddi / Nitric Oxide 70 (2017) 9e24

The Review of DIABETIC STUDIES

REVIEW

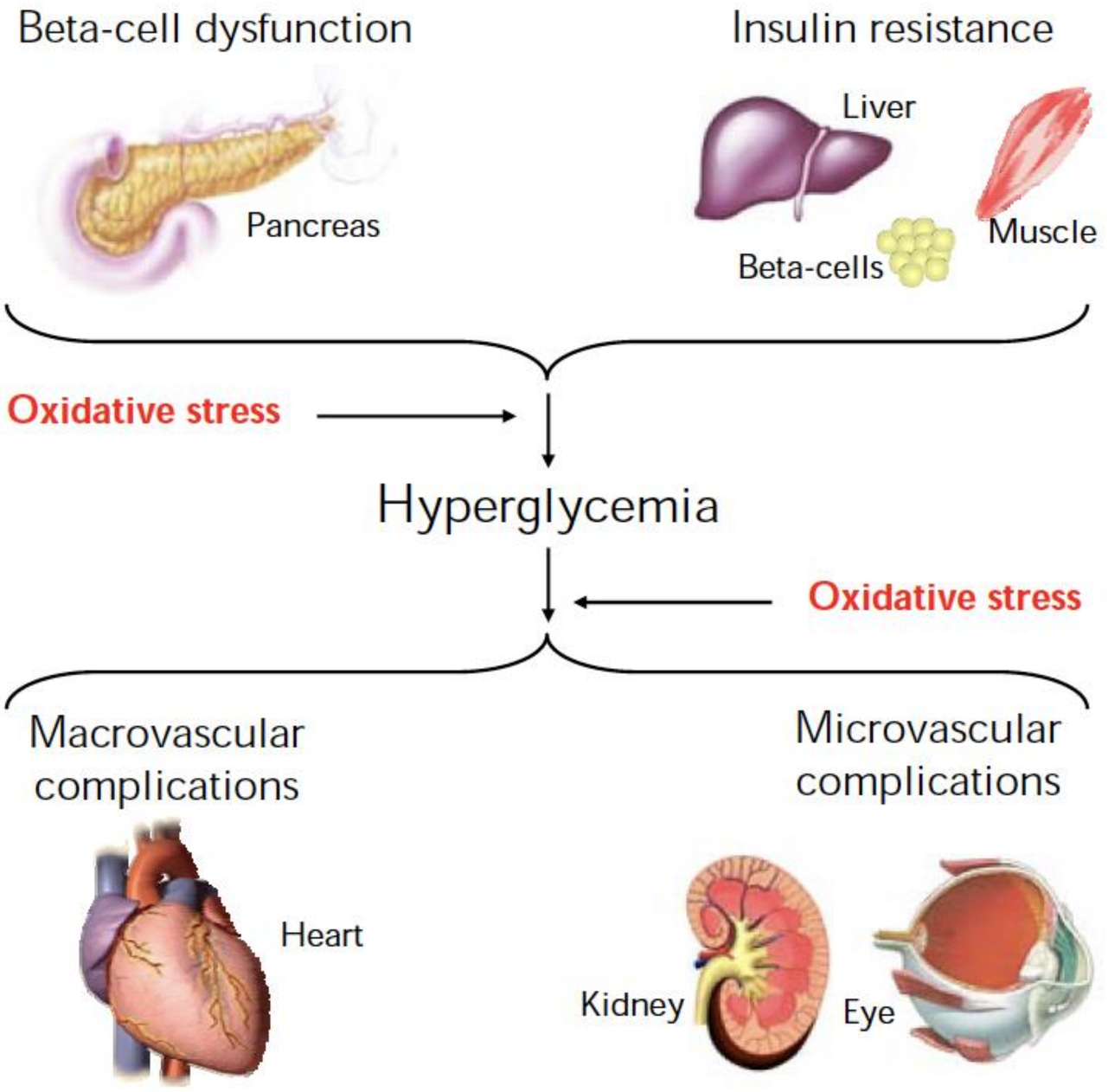
Vol 7 No 1 2010 — Review of Diabetic Studies

Oxidative Stress, Nitric Oxide, and Diabetes

Dario Pitocco[1,2], Francesco Zaccardi[1,2], Enrico Di Stasio[3], Federica Romitelli[3], Stefano A. Santini[3], Cecilia Zuppi[3], and Giovanni Ghirlanda[1]

[1] *Institute of Internal Medicine, Catholic University of Rome, Largo Agostino Gemelli 8, 00168 Rome, Italy.* [2] *Contributed equally to the article.* [3] *Department of Biochemistry, Catholic University of Rome, 00168 Rome, Italy. Address correspondence to: Dario Pitocco, e-mail:*

In the state of oxidative stress, the production of ROS exceeds the available antioxidant defense systems. As a consequence, bioactivity of NO, a paracrine factor that controls the vascular tone, inhibits platelet function, prevents adhesion of leukocytes, and reduces proliferation of the intima (anti-atherosclerotic mechanism). A dominant mechanism reducing the bioavailability of vascular NO relates to its rapid oxidative inactivation by the ROS O2 -. ***In addition, there is evidence that persisting oxidative stress renders eNOS dysfunctional such that it does not produce NO any longer, but O2 instead.***



Rev Diabet Stud (2010) 7:15-25

Current Pharmaceutical Design, 2001, *7*, 881-908

New Issues about Nitric Oxide and its Effects on the Gastrointestinal Tract

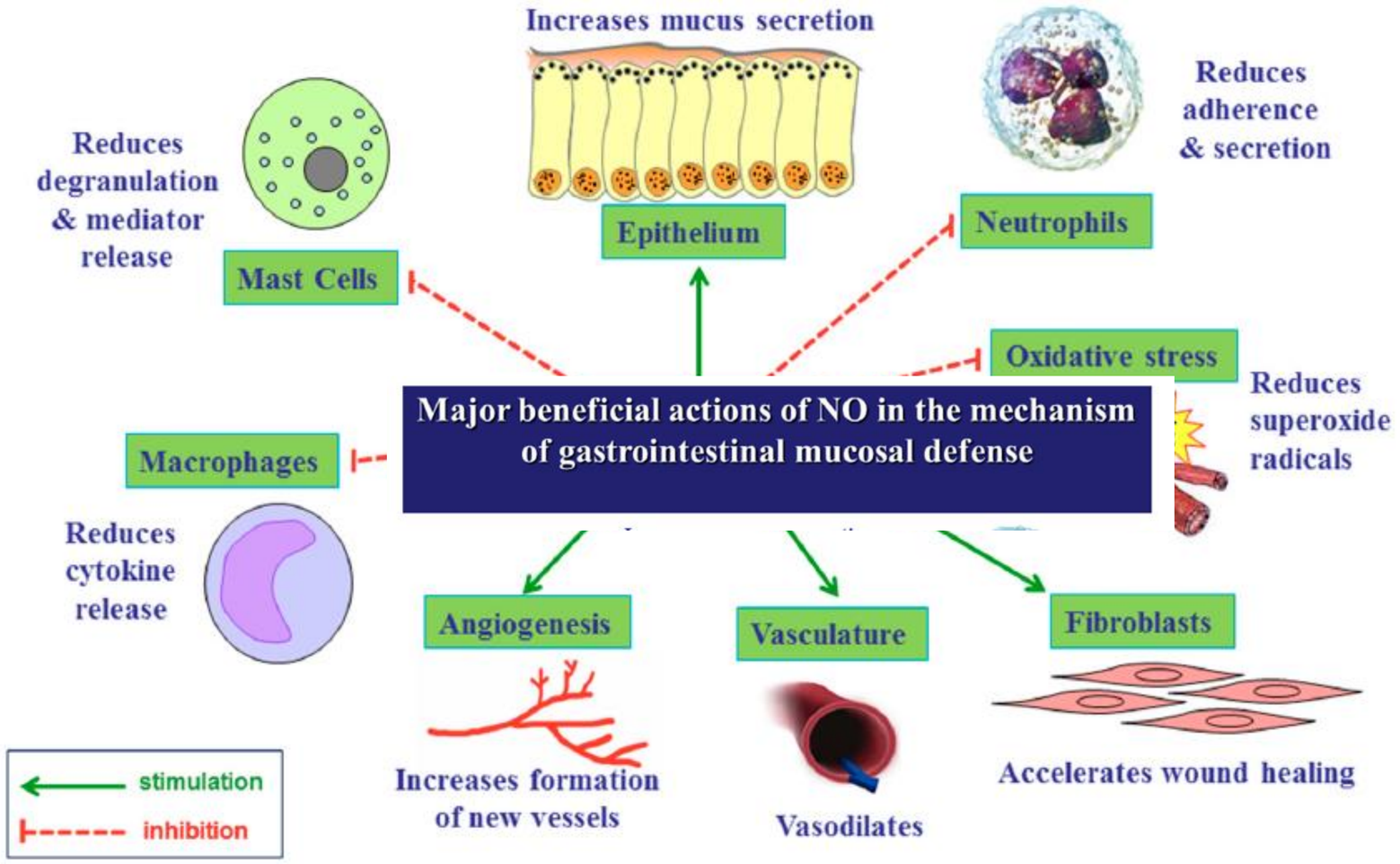
M.J. Martín*, M.D. Jiménez and V. Motilva

Department of Pharmacology, Faculty of Pharmacy, University of Seville, Spain

Abstract: Over the last years the important role of nitric oxide (NO) as endogenous modulator of numerous physiological functions has been shown. NO is involved in the regulation of blood flow, maintenance of vascular tone, control of platelet aggregation, and modulation of the activity of the

gastric mucus secretion, alkaline production, and is involved in the maintenance of mucosal bl

Major beneficial actions of *NO in the mechanism of gastrointestinal mucosal defense



Molecules 2015, 20, 9099-9123; doi:10.3390/molecules20059099

Nitric Oxide 88 (2019) 27–34

Contents lists available at ScienceDirect

Nitric Oxide

journal homepage: www.elsevier.com/locate/yniox

Inorganic nitrate prevents the loss of tight junction proteins and modulates inflammatory events induced by broad-spectrum antibiotics: A role for intestinal microbiota?

Bárbara S. Rocha[a,*], Mariana G. Correia[a], Anabela Pereira[b,c], Isabel Henriques[c,d], Gabriela J. Da Silva[a], João Laranjinha[a]

A B S T R A C T

Upon consumption, dietary nitrate is reduced to nitrite in the oral cavity and to nitric oxide (•NO) in the stomach. Here, •NO increases mucosal blood flow, mucus thickness and prevents microbial infections. However, the impact of nitrate on gut microbiota, a pleiotropic organism essential to maintain gastrointestinal and systemic

y nitrate may be envisaged as a key component of functional foods with beneficial impact on g

and diversity in comparison to controls ($p = 0.0016$). After 7 days of treatment, whereas antibiotics reduced

Physiologic Actions of NO in the Gastrointestinal Tract

- Control of fundic musculature
- Tissue regeneration of the mucosa
- Stimulation of mucus production
- Decrease in the secretory and alkaline production
- Inhibition of leucocyte infiltration
- Maintenance of mucosal blood flow

Nitric Oxide 88 (2019) 27–34

Dietary Nitrate and Nitric Oxide Metabolism: Mouth, Circulation, Skeletal Muscle, and Exercise Performance

ANDREW M. JONES[1], ANNI VANHATALO[1], DOUGLAS R. SEALS[2], MATTHEW J. ROSSMAN[2], BARBORA PIKNOVA[3], and KRISTIN L. JONVIK[4,5]

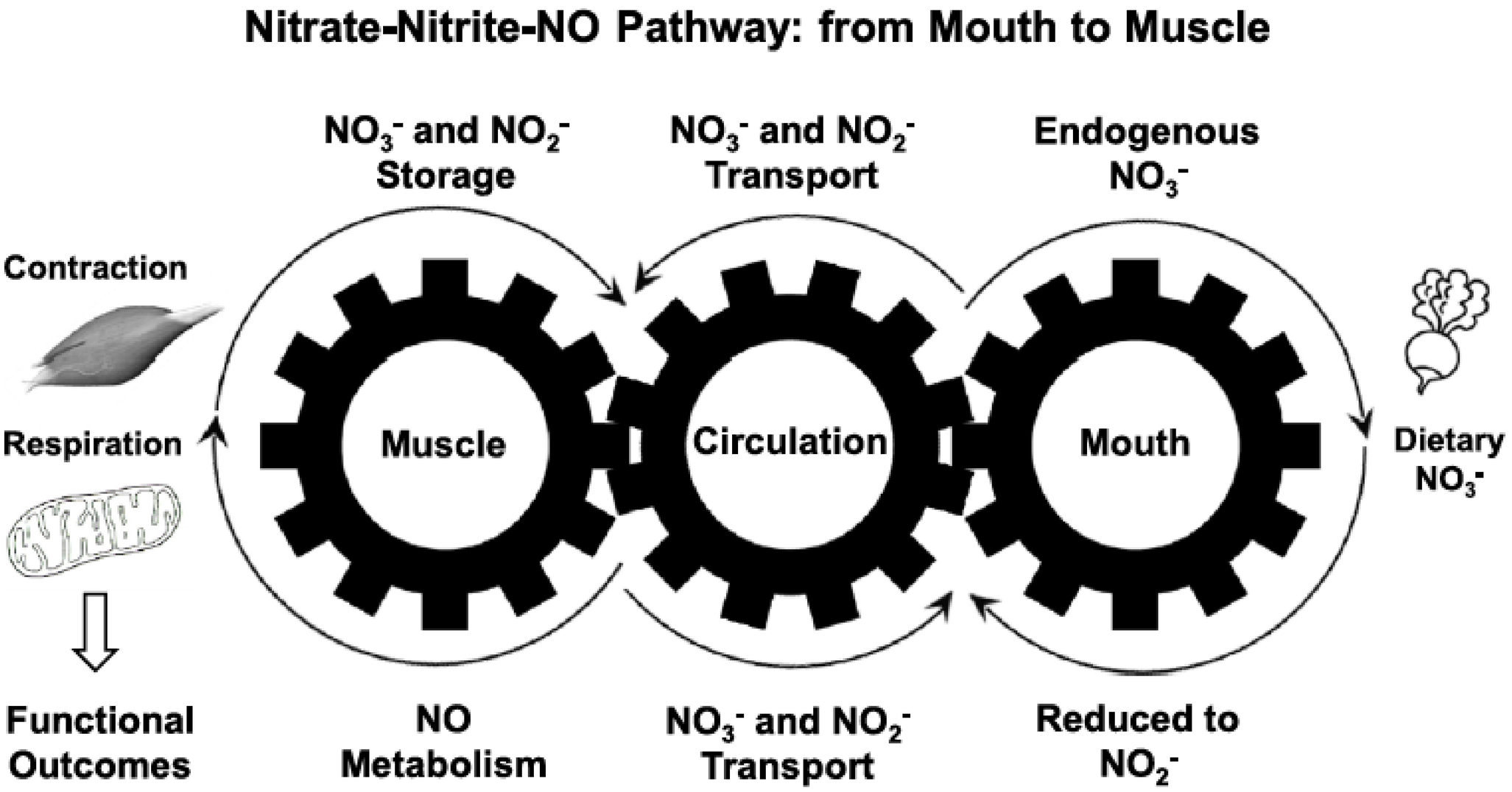
[1]Department of Sport and Health Sciences, University of Exeter, Exeter, UNITED KINGDOM; [2]Department of Integrative Physiology, University of Colorado Boulder, Boulder, CO; [3]Molecular Medicine Branch, National Institute of Diabetes, Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD; [4]Department of Human Biology, NUTRIM School of Nutrition and Translational Research in Metabolism, Maastricht University Medical Centre+, Maastricht, THE NETHERLANDS; and [5]Department of Physical Performance, Norwegian School of Sport Sciences, Oslo, NORWAY

ABSTRACT

JONES, A. M., A. VANHATALO, D. R. SEALS, M. J. ROSSMAN, B. PIKNOVA, and K. L. JONVIK. Dietary Nitrate and Nitric Oxide Metabolism: Mouth, Circulation, Skeletal Muscle, and Exercise Performance. *Med. Sci. Sports Exerc.*, Vol. 53, No. 2, pp. 280–294, 2021. Nitric oxide (NO) is a gaseous signaling molecule that plays an important role in myriad physiological processes, including the regulation

Dietary nitrate supplementation has also been shown to enhance skeletal muscle function and to improve exercise performance in some circumstances. Recently, it has been established that nitrate concentration in skeletal muscle is much higher than that in blood and that muscle nitrate stores are exquisitely sensitive to dietary nitrate supplementation and deprivation.

this review, we consider the possibility that nitrate represents an essential storage form of NO and discuss the integrated function of the oral microbiome, circulation, and skeletal muscle in nitrate–nitrite–NO metabolism, as well as the practical relevance for health and performance.



DOI: 10.1249/MSS.0000000000002470

Dietary nitrate supplementation improves sprint and high-intensity intermittent running performance

Christopher Thompson [a], Anni Vanhatalo [a], Harry Jell [a], Jonathan Fulford [b], James Carter [c], Lara Nyman [c], Stephen J. Bailey [a], Andrew M. Jones [a, *]

[a] *Sport and Health Sciences, University of Exeter, Heavitree Road, Exeter, UK*
[b] *NIHR Exeter Clinical Research Facility, University of Exeter, Heavitree Road, Exeter, UK*
[c] *Gatorade Sports Science Institute, PepsiCo R&D, Barrington, IL, USA*

ARTICLE INFO

Article history:
Received 27 July 2016
Received in revised form
19 October 2016
Accepted 20 October 2016
Available online 21 October 2016

Keywords:
Nitric oxide
Beetroot juice
Running speed

ABSTRACT

The influence of dietary nitrate (NO_3^-) supplementation on indices of maximal sprint and intermittent exercise performance is unclear.
Purpose: To investigate the effects of NO_3^- supplementation on sprint running performance, and cognitive function and exercise performance during the sport-specific Yo-Yo Intermittent Recovery level 1 test (IR1).
Methods: In a double-blind, randomized, crossover study, 36 male team-sport players received NO_3^--rich (BR; 70 mL·day^{-1}; 6.4 mmol of NO_3^-), and NO_3^--depleted (PL; 70 mL·day^{-1}; 0.04 mmol NO_3^-) beetroot juice for 5 days. On day 5 of supplementation, subjects completed a series of maximal 20-m sprints followed by the Yo-Yo IR1. Cognitive tasks were completed prior to, during and immediately following the Yo-Yo IR1.

Therefore, these findings indicate that short-term dietary NO3 supplementation can improve performance during short-duration maximal sprint running and high-intensity intermittent running, and support the notion that NO3 supplementation might enhance team sport performance.

has the potential to improve performance in single-sprint or multiple-sprint (team) sports.

*Fig. 1. BR elevated plasma [NO2] by 248% compared to baseline and 226% compared to PL (panel A). BR elevated plasma [NO3] by 710% compared to baseline and 666% compared to PL (panel B). *P < 0.001 compared to PL; #P < 0.001 compared to baseline.*

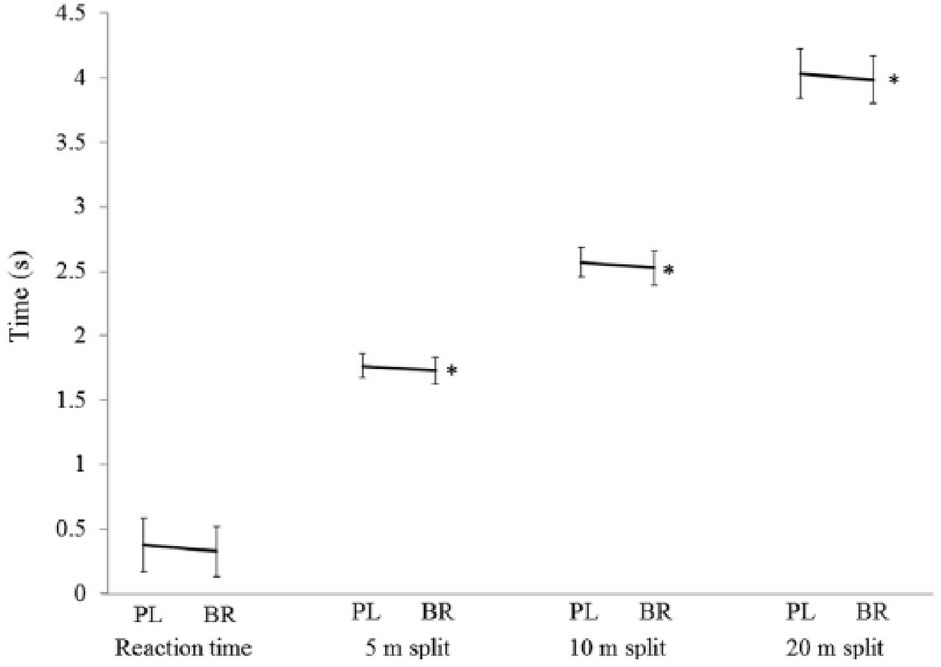
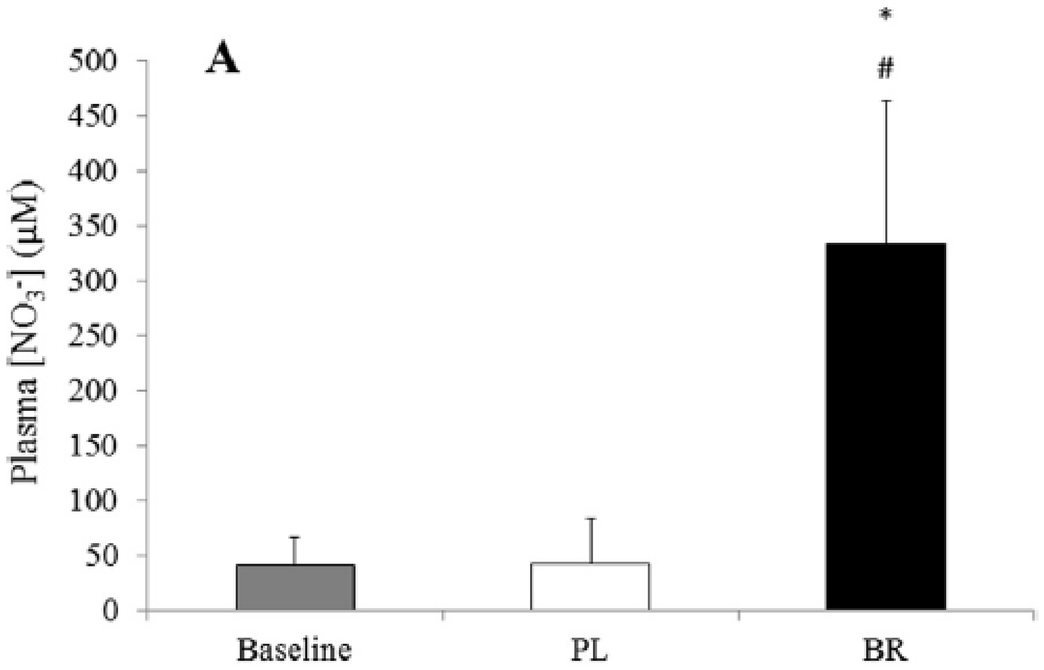
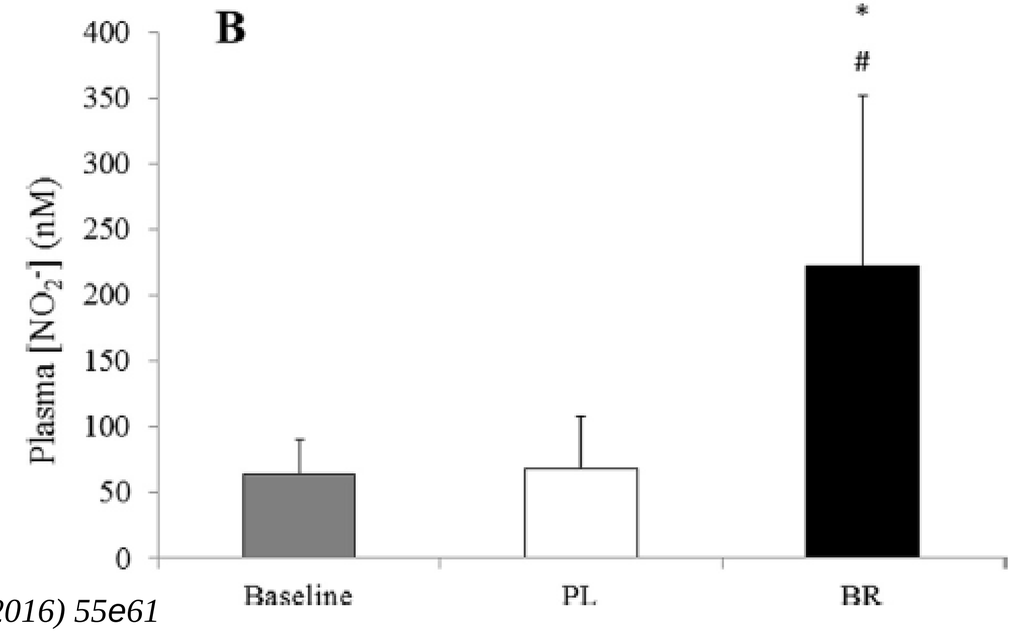


Fig. 2. Sprint performance was improved in BR compared to PL. *P < 0.05.





ESSAY

ADVANCED SCIENCE Open Access

www.advancedscience.com

Nitric Oxide to Fight Viral Infections

Fabio Lisi, Alexander N. Zelikin, and Rona Chandrawati**

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) that has quickly and deeply affected the world, with over 60 million confirmed cases. There has been a great effort worldwide to contain the virus and to search for an effective treatment for patients who become critically ill with COVID-19. A promising therapeutic compound currently undergoing clinical trials for

fight viral infections are suggested.

A promising therapeutic compound currently undergoing clinical trials for COVID-19 is nitric oxide (NO), which is a free radical that has been previously reported to inhibit the replication of several DNA and RNA viruses, including coronaviruses. Although NO has potent antiviral activity, it has a complex role in the immunological host responses to viral infections, i.e., it can be essential for pathogen control or detrimental for the host, depending on its concentration and the type of virus.

et al., at least 65% of recent major human infectious disease outbreaks have originated from zoonotic viruses,[3] including: acquired immune deficiency syndrome (AIDS), severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS), Ebola, swine influenza, avian influenza, dengue fever, and zika fever. Coro-

ation of the smooth muscles in the lungs to open airways),[5,6] vasodilation (widening of blood vessels to increase blood flow),[7–9]

Adv. Sci. 2021, 8, 2003895: 10.1002/advs.202003895

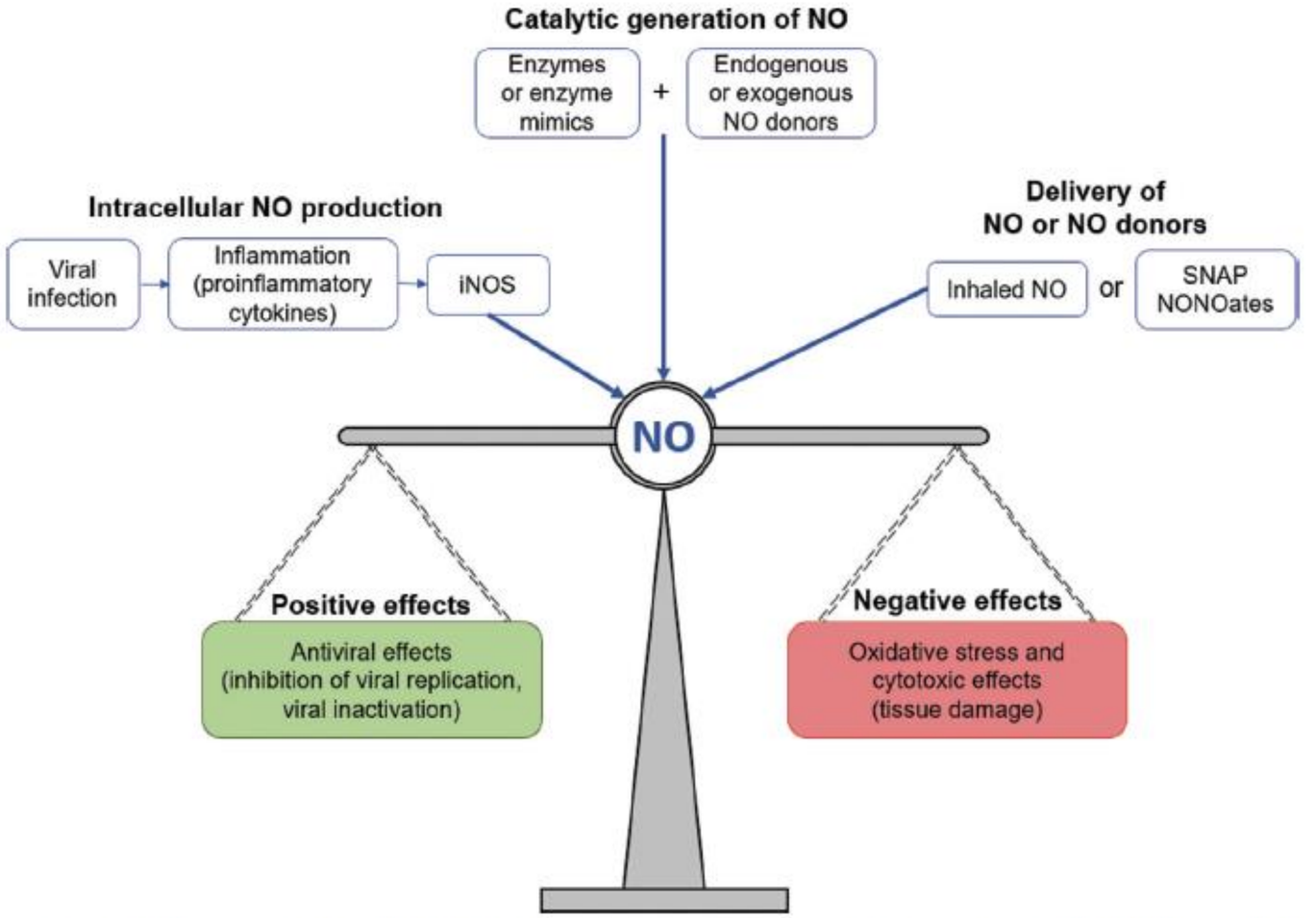


Figure 1. A general overview of the role of nitric oxide (NO) during viral infections, where the radical is involved in the modulation of the immune response. In the body, NO can be: synthesized within various cell types by the enzyme iNOS; generated from endogenous or exogenous NO donors using enzymes or enzyme mimics; delivered by the administration of exogenous NO donors. The overall effect of NO activity can either be positive (pathogen control) or negative (disease promoting), depending on the pathogen, the concentrations of the radical, and for how long NO is produced.

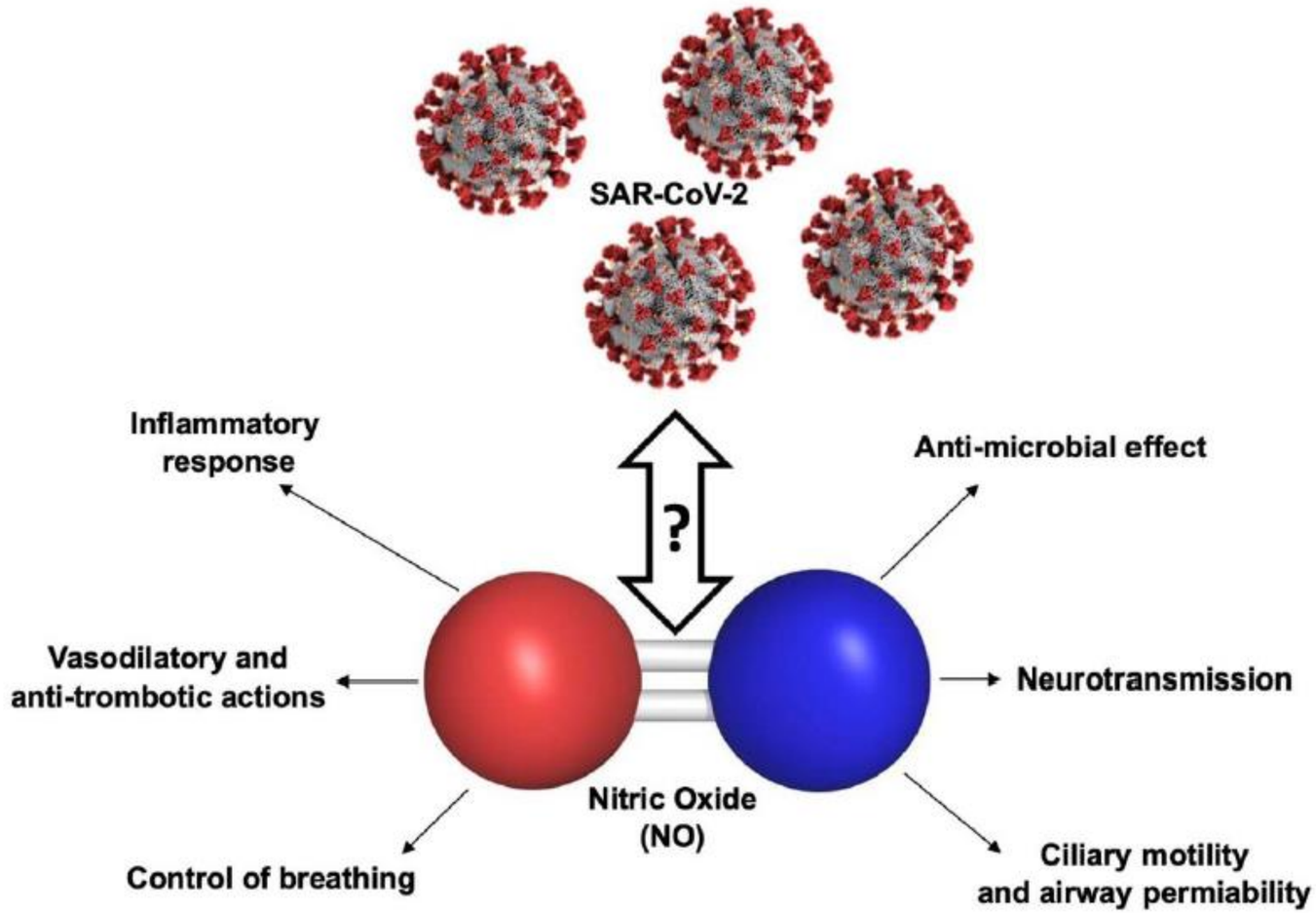


Figure 1. Physiologic effects of Nitric Oxide (NO) that may have relevance in the prevention and treatment of SARS-Cov-2 infection. Further research is needed to investigate the interplay between the NO molecule and the virus responsible for COVID-19 infection.

molecules

MDPI

Review

An Overview of NO Signaling Pathways in Aging

Ali Mohammad Pourbagher-Shahri [1], Tahereh Farkhondeh [2,3], Marjan Talebi [4], Dalia M. Kopustinskiene [5], Saeed Samarghandian [6,*] and Jurga Bernatoniene [5,7,*]

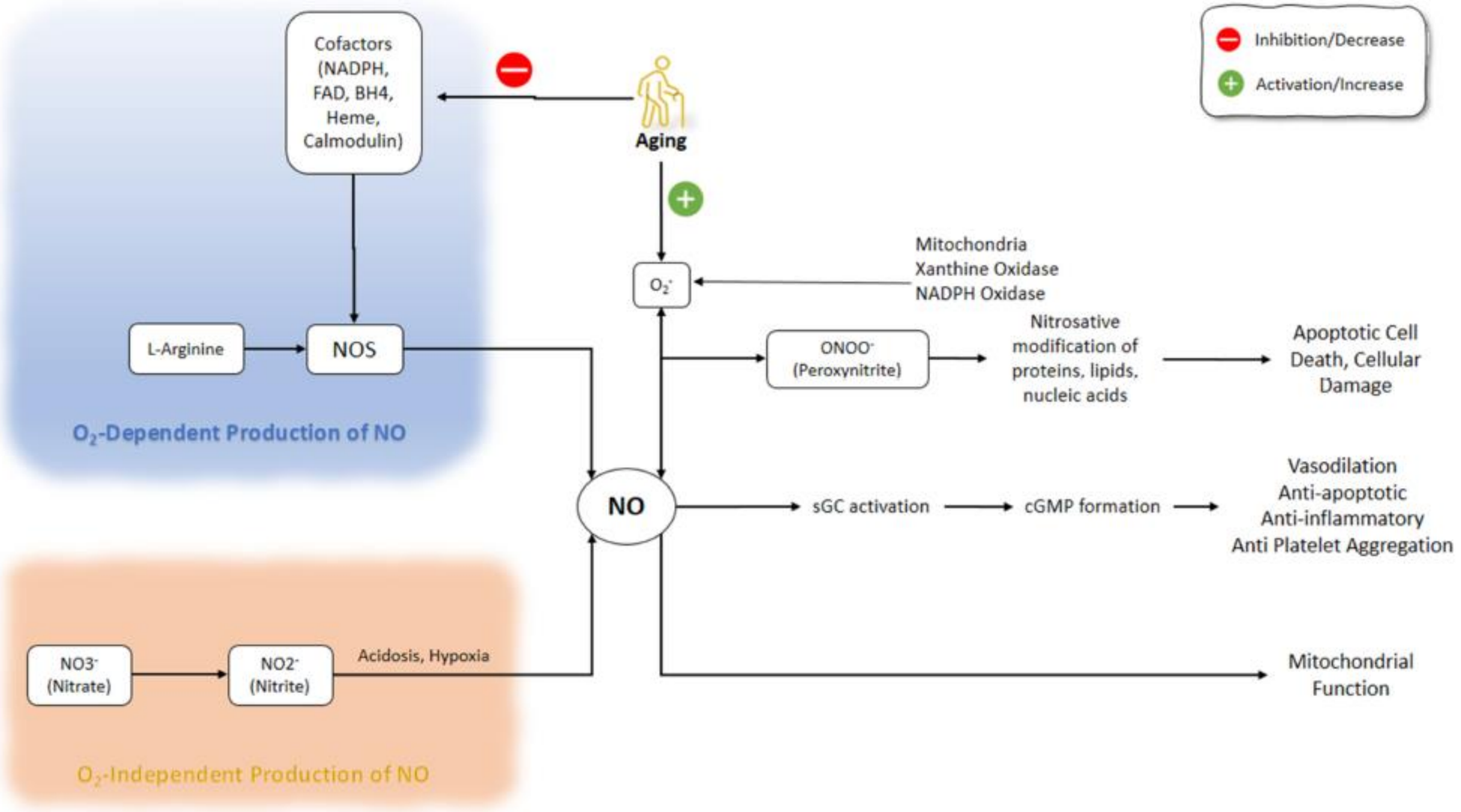
Abstract: Nitric Oxide (NO) is a potent signaling molecule involved in the regulation of various cellular mechanisms and pathways under normal and pathological conditions. NO production, its effects, and its efficacy, are extremely sensitive to aging-related changes in the cells. Herein, we review the mechanisms of NO signaling in the cardiovascular system, central nervous system (CNS), reproduction system, as well as its effects on skin, kidneys, thyroid, muscles, and on the immune system during aging. The aging-related decline in NO levels and bioavailability is also discussed in

Citation: Pourbagher-Shahri, A.M.; Farkhondeh, T.; Talebi, M.; Kopustinskiene, D.M.;

The decreased NO production by endothelial nitric oxide synthase (eNOS) was revealed in the aged cardiovascular system. In the CNS, the decline of the neuronal (n)NOS production of NO was related to the impairment of memory, sleep, and cognition. NO played an important role in the aging of oocytes and aged-induced erectile dysfunction. Aging down-regulated NO signaling pathways in endothelial cells resulting in skin, kidney, thyroid, and muscle disorders.

Published: 27 July 2021

tic agents


Cofactors (NADPH, FAD, BH4, Heme, Calmodulin)
Aging
Inhibition/Decrease
Activation/Increase
Mitochondria
Xanthine Oxidase
NADPH Oxidase
O_2^-
L-Arginine
NOS
ONOO⁻ (Peroxynitrite)
Nitrosative modification of proteins, lipids, nucleic acids
Apoptotic Cell Death, Cellular Damage
O_2-Dependent Production of NO
NO
sGC activation
cGMP formation
Vasodilation
Anti-apoptotic
Anti-inflammatory
Anti Platelet Aggregation
NO3⁻ (Nitrate)
NO2⁻ (Nitrite)
Acidosis, Hypoxia
Mitochondrial Function
O_2-Independent Production of NO

Published in final edited form as:
J Sex Med. 2009 March 1; 6(S3PROCEEDINGS): 247–253. doi:10.1111/j.1743-6109.2008.01122.x.

Endothelial Nitric Oxide Synthase Regulation in Female Genital Tract Structures

Biljana Musicki, PhD, **Tongyun Liu, MS**, **Gwen A. Lagoda, MS**, **Trinity J. Bivalacqua, MD, PhD**, **Travis D. Strong, BA**, and **Arthur L. Burnett, MD**
Department of Urology, The Johns Hopkins University, Baltimore, MD, USA

Abstract

Introduction—Female sexual arousal disorder (FSAD) is a major component of female sexual dysfunctions, affecting 25–70% of women. The mechanisms of FSAD are poorly understood. Estrogen contributes to the control of genital blood flow during the sexual response. Vascular effects of estrogen are mostly attributed to its regulation of endothelial nitric oxide (NO) production. However, the role of endothelial NO synthase (eNOS) and the mechanisms that regulate eNOS in

y sexual arousal. In view of the key role of endothelial NO in smooth muscle relaxation and vas

Pharmacological Reports
2013, 65, 1655–1662
ISSN 1734-1140

Review

Cytokines, prostaglandins and nitric oxide in the regulation of stress-response systems

Anna Gądek-Michalska, Joanna Tadeusz, Paulina Rachwalska, Jan Bugajski

Department of Physiology, Institute of Pharmacology, Polish Academy of Sciences, Smętna 12, PL 31-343 Kraków, Poland

Abstract:
Hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis is accepted as one of the fundamental biological mechanisms that underlie major depression. This hyperactivity is caused by diminished feedback inhibition of glucocorticoid (GC)-induced reduction of HPA axis signaling and increased corticotrophin-releasing hormone (CRH) secretion from the hypothalamic paraventricular nucleus (PVN) and extra-hypothalamic neurons. During chronic stress-induced inhibition of systemic feedback, cytosolic glucocorticoid receptor (GR) levels were significantly changed in the prefrontal cortex (PFC) and hippocampus, both structures known to be deeply involved in the pathogenesis of depression.
Cytokines secreted by both immune and non-immune cells can markedly affect neurotransmission within regulatory brain circuits related to the expression of emotions; cytokines may also induce hormonal changes similar to those observed following exposure to

physiological and pathological processes. Neuronal NO synthase (nNOS) modulates learn

The Link Between Erectile and Cardiovascular Health: The Canary in the Coal Mine

David R. Meldrum, MD[a,*], Joseph C. Gambone, DO, MPH[a], Marge A. Morris, MEd, RD, CDE[c], Donald A.N. Meldrum, MD[d], Katherine Esposito, MD, PhD[e], and Louis J. Ignarro, PhD[b]

Lifestyle and nutrition have been increasingly recognized as central factors influencing vascular nitric oxide (NO) production and erectile function. This review underscores the importance of NO as the principal mediator influencing cardiovascular health and erectile function. Erectile dysfunction (ED) is associated with smoking, excessive alcohol intake, physical inactivity, abdominal obesity, diabetes, hypertension, and decreased antioxidant defenses, all of which reduce NO production. Better lifestyle choices; physical exercise; improved nutrition and weight control; adequate intake of or supplementation with omega-3 fatty acids, antioxidants, calcium, and folic acid; and replacement of any testosterone deficiency will all improve vascular and erectile function and the response to phosphodiesterase-5 inhibitors, which also increase vascular NO production. More frequent penile-specific exercise improves local endothelial NO production. Excessive intake of vitamin E,

Erectile dysfunction (ED) is associated with smoking, excessive alcohol intake, physical inactivity, abdominal obesity, diabetes, hypertension, and decreased antioxidant defenses, all of which reduce NO production. Better lifestyle choices; physical exercise; improved nutrition and weight control; adequate intake of or supplementation with omega-3 fatty acids, antioxidants, calcium, and folic acid; and replacement of any testosterone deficiency will all improve vascular and erectile function…

Factors influencing *NO production and erectile function

- Exercise
- High nitrate diet
- L-arginine
- Omega 3 EFA
- Antioxidants, Vitamin C & E
- Weight reduction
- Folic acid
- Moderate alcohol

Meldrum, DR, et el, The Link Between Erectile and Cardiovascular Health: The Canary in the Coal Mine. The American Journal of Cardiology doi:10.1016/j.amjcard.2011.03.093

Physiology & Behavior xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Physiology & Behavior

journal homepage: www.elsevier.com/locate/phb

Dietary nitrate modulates cerebral blood flow parameters and cognitive performance in humans: A double-blind, placebo-controlled, crossover investigation☆,☆☆

Emma L. Wightman [a], Crystal F. Haskell-Ramsay [a], Kevin Thompson [b,1], Jamie R. Blackwell [c], Paul G. Winyard [d], Joanne Forster [a], Andrew M. Jones [c], David O. Kennedy [a,*]

[a] Brain, Performance and Nutrition Research Centre, School of Life Sciences, Northumbria University, Newcastle upon Tyne NE1 8ST, United Kingdom
[b] Sport, Exercise and Wellbeing Research Centre, School of Life Sciences, Northumbria University, Newcastle upon Tyne NE1 8ST, United Kingdom
[c] School of Sport and Health Sciences, St. Luke's Campus, University of Exeter, Exeter EX1 2LU, United Kingdom
[d] Peninsula College of Medicine and Dentistry, St. Luke's Campus, University of Exeter, Exeter EX1 2LU, United Kingdom

te can modulate the CBF response to task performance and potentially improve cognitive perform

NIH Public Access
Author Manuscript
Nitric Oxide. Author manuscript; available in PMC 2012 January 1.

Published in final edited form as:
Nitric Oxide. 2011 January 1; 24(1): 34–42. doi:10.1016/j.niox.2010.10.002.

Acute effect of a high nitrate diet on brain perfusion in older adults

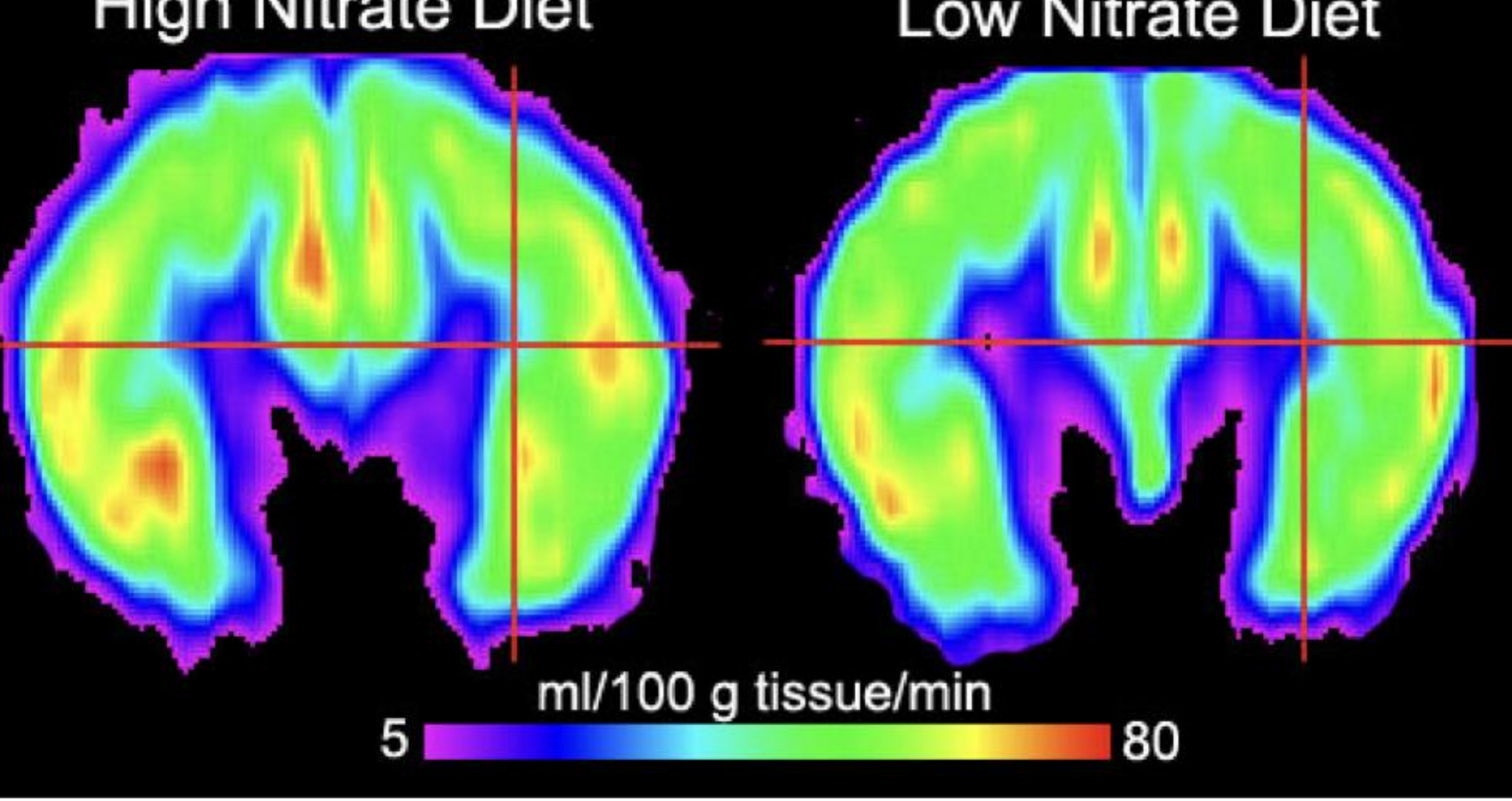
Tennille D. Presley[1,2], **Ashley R. Morgan**[3], **Erika Bechtold**[4], **William Clodfelter**[4], **Robin W. Dove**[2,5], **Janine M. Jennings**[2,5], **Robert A. Kraft**[6], **S. Bruce King**[2,4], **Paul J. Laurienti**[2,3], **W. Jack Rejeski**[2,7], **Jonathan H. Burdette**[2,3,*], **Daniel B. Kim-Shapiro**[1,2,*], and **Gary D. Miller**[2,7,*]

Abstract

Aims—Poor blood flow and hypoxia/ischemia contribute to many disease states and may also be a factor in the decline of physical and cognitive function in aging. Nitrite has been discovered to be a vasodilator that is preferentially harnessed in hypoxia. Thus, both infused and inhaled nitrite

As already discussed, nitrite has been shown to not only increase blood flow to certain areas of the body, **but also acts preferentially in hypoxic conditions, allowing nitrite to increase blood flow precisely in the areas where it is needed.**

Based on this notion, our data suggest that a diet high in nitrate might allow increased perfusion to those areas of the brain known to be at risk in the elderly and important for cognitive function —the deep white matter in the frontal lobe.



Nitric Oxide. 2011 January 1; 24(1): 34–42. doi:10.1016/j.niox.2010.10.002.

Dietary Nitrate

- Reduce hypertension
- Improve exercise performance
- Improved cerebral blood flow, esp frontal lobes
- Improved cognitive function.

Journal of Clinical and Diagnostic Research. 2016 Jul, Vol-10(7): CC01-CC05.

Clinical Study

Effects of Dietary Nitrates on Systemic and Cerebrovascular Hemodynamics

Vernon Bond Jr.,[1] Bryan H. Curry,[2] Richard G. Adams,[2] M. Sadegh Asadi,[3] Richard M. Millis,[4] and Georges E. Haddad[4]

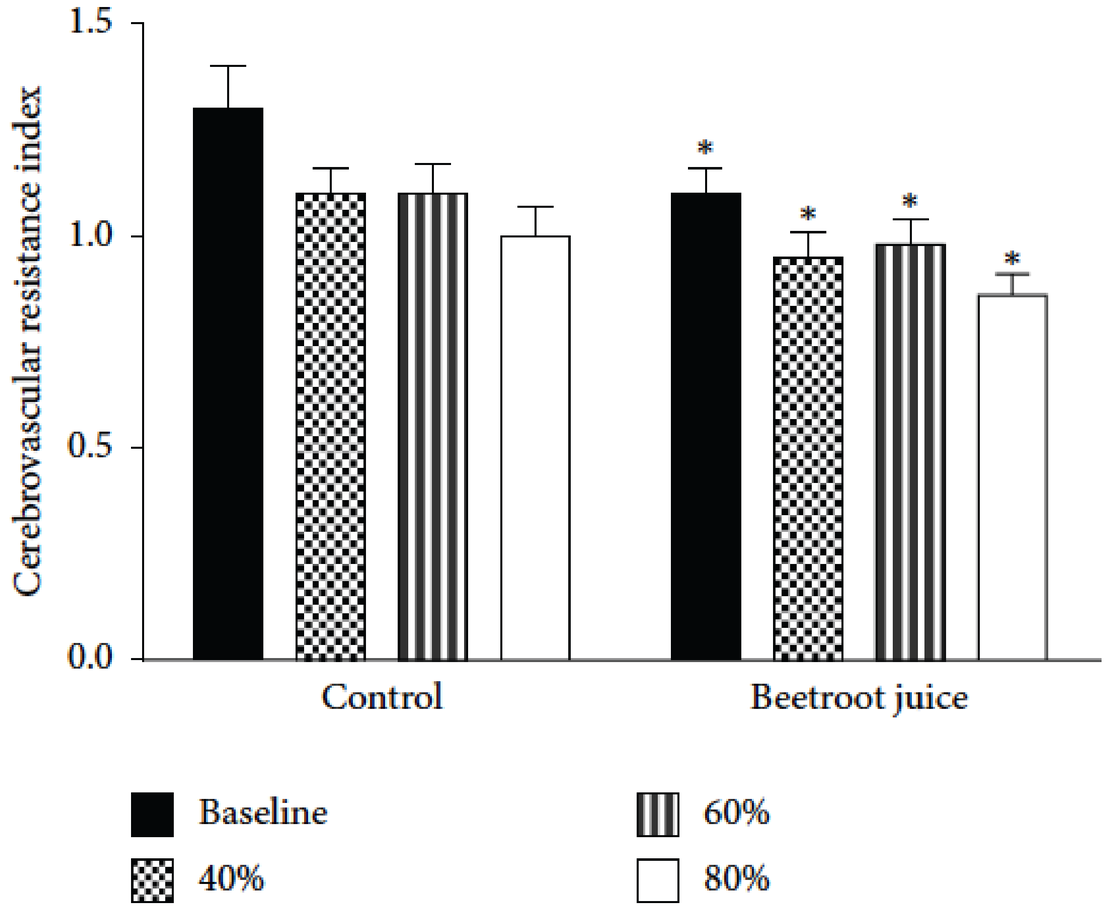
[1] *Department of Health, Human Performance & Leisure Studies and the Cancer Center Physical Medicine & Nutrition Laboratory, Howard University, Washington, DC 20059, USA*
[2] *Department of Medicine, Division of Cardiology, Howard University Hospital, Washington, DC 20060, USA*
[3] *Department of Neurology, Howard University Hospital, Washington, DC 20060, USA*
[4] *Department of Physiology & Biophysics, Howard University College of Medicine, Washington, DC 20059, USA*

Correspondence should be addressed to Richard M. Millis; rickmillis@aol.com

Received 12 August 2013; Revised 2 October 2013; Accepted 3 October 2013

The findings of this study suggest that the physiological mechanisms underlying dietary nitrate-induced improvements in systemic and cerebral vascular hemodynamics may be some what workload dependent. The hemodynamic improvements associated with the beetroot juice treatment appear to be consistent with counteracting some of the pathophysiologic cerebral vascular features of hypertension, Alzheimer's, and other diseases associated with brain hypo-perfusion and cognitive deficits.

Reference: Bond Jr. V, et el, Effects of Dietary Nitrates on Systemic andCerebrovascular Hemodynamics Research and Practice Volume 2013, Article ID 435629, 9 pages http://dx.doi.org/10.1155/2013/435629



Cardiovascular Resistance Index

Table 2: Effects of beetroot juice treatment at rest.

Variable	Control	Beetroot juice
Nitric oxide (nM)	4.5 ± 1.0	17.8 ± 2.6*
Cardiac output ($L \cdot min^{-1}$)	4.8 ± 0.1	4.9 ± 0.1
Oxygen consumption ($mL \cdot kg^{-1} \cdot min^{-1}$)	4.5 ± 1.0	4.0 ± 0.5
Systolic blood pressure (mm Hg)	119.8 ± 2.8	114.8 ± 2.1*
Diastolic blood pressure (mm Hg)	90.0 ± 2.4	86.4 ± 1.3
Mean blood pressure (mm Hg)	99.6 ± 2.4	95.3 ± 1.4*
Heart rate ($b \cdot min^{-1}$)	85.8 ± 3.2	82.5 ± 3.0
Heart rate-systolic pressure product	10,785 ± 414	9,751 ± 226*

Values expressed in mean ± standard error, measured at rest (baseline).
*Significantly different from control at $P < 0.05$.

Effects of nitrate supplement treatment at rest

Causes of Low Nitric Oxide

- Age????
- Physical inactivity
- Stress…(but can increase iNOS)
- SAD diet: decreased nitrates
- Achlorhydria
- Oral dysbiosis
- Medications and Toxicants
  - Antibiotics & antifungal
  - Antidepressants
  - Oral contraceptives
  - NSAIDs/Cox2 inhibitors
  - Antiseptic mouthwash & Fluoride
  - PPIs
  - Pollutants esp. glyphosate

J PREV MED HYG 2022; 63(SUPPL. 3): E239-E245 OPEN ACCESS

REVIEW

Dietary supplements for improving nitric-oxide synthesis

AYSHA KARIM KIANI[1], GABRIELE BONETTI[2,*], MARIA CHIARA MEDORI[2], PAOLA CARUSO[3], PAOLO MANGANOTTI[3], FRANCESCO FIORETTI[4], SAVINA NODARI[4], STEPHEN THADDEUS CONNELLY[5], MATTEO BERTELLI[1,2,6]
[1] MAGI Euregio, Bolzano, Italy; [2] MAGI'S LAB, Rovereto (TN), Italy; [3] Clinical Unit of Neurology, Department of Medicine, Surgery and Health Sciences, Cattinara University Hospital ASUGI, University of Trieste, Trieste, Italy; [4] Department of Cardiology, University of Brescia and ASST "Spedali Civili" Hospital, Brescia, Italy; [5] San Francisco Veterans Affairs Health Care System, University of California, San Francisco, CA, USA; [6] MAGISNAT, Peachtree Corners (GA), USA

Keywords

Nitric oxide supplementation • Nitric oxide synthesis • L-arginine supplementation • L- citrulline supplementation • Dietary supplements

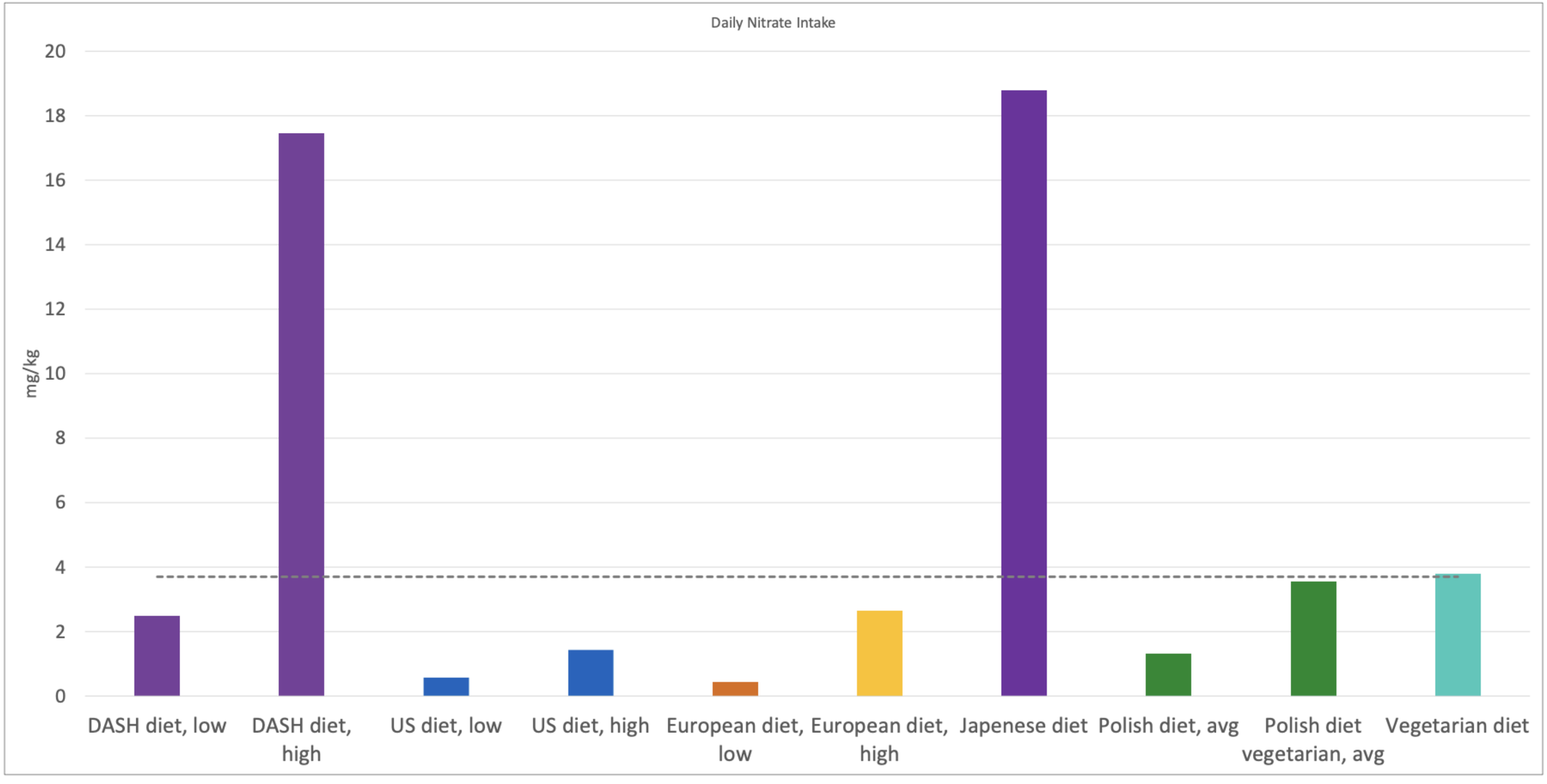
Summary

Nitric oxide (NO) is an essential component of the human body, involved in blood vessel dilation, stimulation of hormone release, ginine precursor that is further converted to NO by a reaction catalyzed by NO synthase. L-arginine supplements increase respi-

ac health, enhances performance during exercise, reduces high blood pressure during pregnanc
Although NO supplementation may have mild to moderate side-effects, using smaller or divided

involved in NO synthesis, whereas L-citrulline acts as an L-ar- under medical supervision.

Comparison of Daily Nitrate Intake Values



The data presented above was collected from published literature as follows: DASH, US, and European diets as cited in Hord et al, 2009; Japanese diet as presented in Sobko, et al 2010; Polish diets as presented and cited in Mitek et al 2013; and Vegetarian diet as cited in Lidder and We bb, 2012.

Regional Differences In Conventional Vegetable Nitrate Values

Table 2. Mean nitrate (NO_3?) concentrations[a] (ppm)[b] of raw vegetables classified as conventional from each city

Product category	Chicago	Dallas	Los Angeles	New York	Raleigh
Broccoli	271 ± 89 (61-822)	357 ± 50 (165-664)	512 ± 85 (164-1140)	279 ± 80 (29-1009)	553 ± 28 (374-680)
Cabbage	475 ± 46 (256-670)	256 ± 33 (63-434)	800 ± 142 (275-1831)	193 ± 28 (37-283)	364 ± 79 (72-882)
Celery	230 ± 19 (147-359)	2052 ± 156 (918-2973)	2651 ± 339 (608-4269)	88 ± 17 (20-157)	2201 ± 112 (1397-2727)
Lettuce	207 ± 32 (79-425)	1370 ± 93 (870-1909)	1051 ± 122 (422-1495)	568 ± 93 (321-970)	986 ± 185 (450-2171)
Spinach	647 ± 69 (162-875)	4923 ± 327 (2377-6473)	4138 ± 451 (2141-8000)	564 ± 174 (65-1545)	3155 ± 145 (2478-4168)

[a]Mean value with standard error; minimum and maximum nitrate values in parentheses.
[b]mg/ kg of fresh weight.

Dietary inorganic nitrate reverses features of metabolic syndrome in endothelial nitric oxide synthase-deficient mice

Mattias Carlström[a,b], Filip J. Larsen[a], Thomas Nyström[c], Michael Hezel[a], Sara Borniquel[a], Eddie Weitzberg[a,1,2], and Jon O. Lundberg[a,1,2]

[a]Department of Physiology and Pharmacology, Karolinska Institutet, SE-171 77 Stockholm, Sweden; [b]Department of Medical Cell Biology, Division of Integrative Physiology, Uppsala University, SE-75123 Uppsala, Sweden; and [c]Department of Clinical Science and Education, Division of Internal Medicine, Unit for Diabetes Research, Karolinska Institutet, Södersjukhuset, SE-118 83 Stockholm, Sweden

Edited* by Louis J. Ignarro, University of California Los Angeles School of Medicine, Los Angeles, CA, and approved September 7, 2010 (received for review June 23, 2010)

The metabolic syndrome is a clustering of risk factors of metabolic origin that increase the risk for cardiovascular disease and type 2 diabetes. A proposed central event in metabolic syndrome is a decrease in the amount of bioavailable nitric oxide (NO) from endothelial NO synthase (eNOS). Recently, an alternative pathway for NO formation in mammals was described where inorganic nitrate, a supposedly inert NO oxidation product and unwanted dietary constituent, is serially reduced to nitrite and then NO and other bioactive nitrogen oxides. Here we show that several features of metabolic syndrome that develop in eNOS-deficient mice can be reversed by dietary supplementation with sodium nitrate, in

strategies against cardiovascular disease and type 2 diabetes.

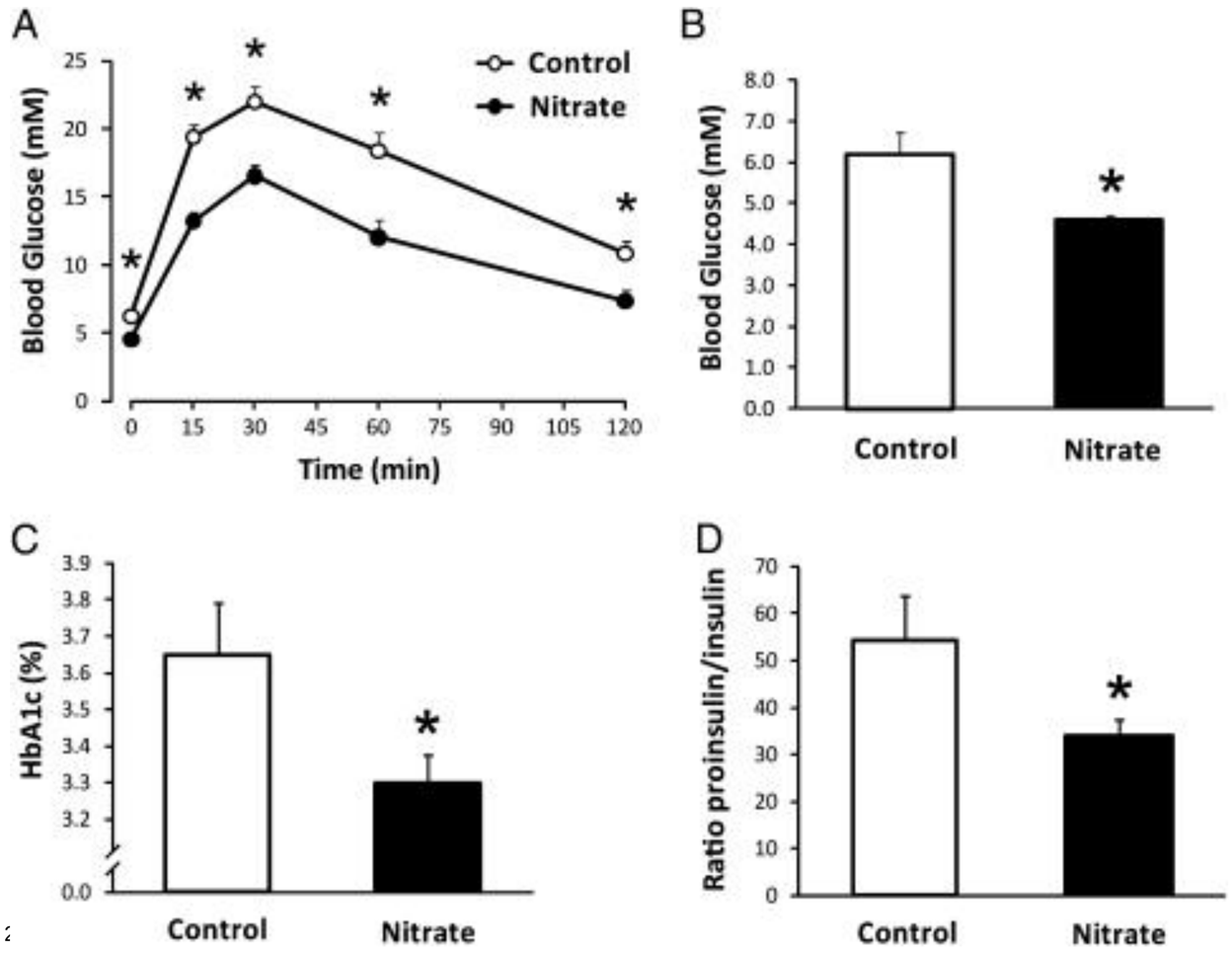
intermediate (16, 18) and this more reactive compound is further metabolized to NO, nitrosothiols, and other bioactive nitrogen oxides via numerous enzymatic and nonenzymatic pathways in blood and tissues (10). Interestingly, our everyday diet represents a major source of inorganic nitrate, and vegetables are particularly rich in this anion. It has been speculated (10, 11) that the high nitrate content in vegetables contributes to the well-known cardioprotective effects of this food group.

The aim of the present study was to investigate whether administration of sodium nitrate would result in formation of bioactive nitrogen oxides in vivo and whether chronic dietary nitrate

Here we show that several features of metabolic syndrome that develop in eNOS-deficient mice can be reversed by dietary supplementation with sodium nitrate, in amounts similar to those derived from eNOS under normal conditions. In humans, this dose corresponds to a rich intake of vegetables, the dominant dietary nitrate source.

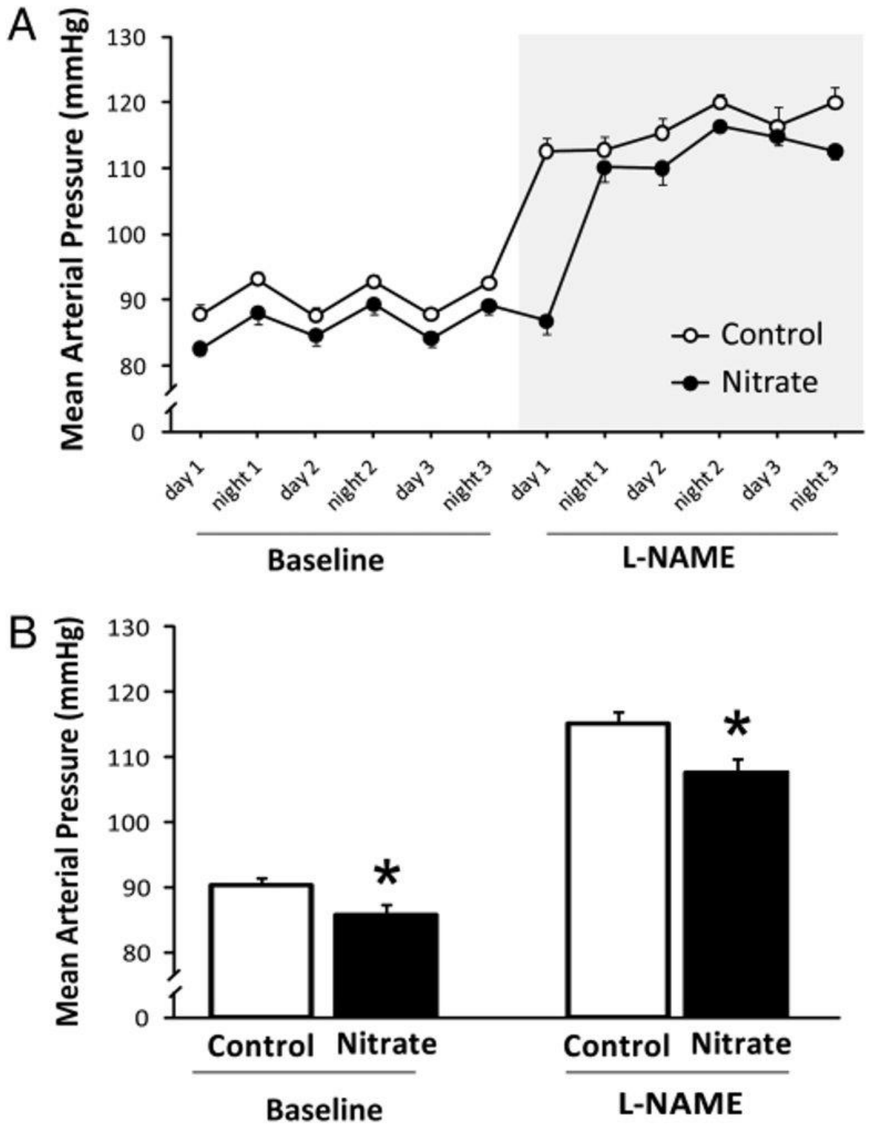
could be detected in liver tissue (Fig. 1 *A–C*). Next, we measured

Dietary Nitrate **Improves Glucose Tolerance** and **Reduces Fasting Blood Glucose** in eNOS-deficient Mice.



Carlstrom et al, Proc Natl Acad Sci U S A. 2
October 12; 107(41): 17716–17720.

Effects of **Dietary Nitrate** on **Blood Pressure**



water (control) or water supplemented with sodium nitrate (0.1 mmol·kg−1·d−1) for 8 wk

Carlstrom et al, Proc Natl Acad Sci U S A. 2010 October 12; 107(41): 17716–17720.

Carol Grant

Instructions:
Monitor Bp at various times; Two NO capsules at lunch; testing two hours afterwards; second niacin for Carol at breakfast (one taken at dinner regularly)

DATE	BP/Time	NO Result	BP/Time	NO Result
Mon, 11-7-22	124/78 L up 9:18am 117/95 R dn 9:24am	X	141/80 L dn 9:21am 135/87 R up 9:23am	X
Tues, 11-8	116/75 R dn 4:50pm 126/89 L up 4:52pm	X	137/64 L dn 6:04pm 128/77 R up 6:08pm	X
Wed, 11-9*	117/74 L dn 7:27pm 129/88 R up 7:30pm	X	128/67 L dn 7:32pm 131/73 R up 7:34pm	X
Thur, 11-10*	112/82 R dn 1:29pm 20/80 L up 1:21pm	220	109/67 R dn 2:05pm 112/69 L up 2:08pm	110
Fri, 11-11*	skipped		skipped	
Sat 11-12*	125/89 R up 9:10pm 119/76 L dn 9:13pm	X	143/83 L dn 9:20pm 131/82 R up 9:30pm	X
Sun, 11-13*	117/89 L up 8:13am 128/90 R dn 8:18am	X	130/64 L up 8:48am 131/78 R dn 8:20am	X
Mon, 11-14*	120/89 R up 9:25am 121/77 L dn 9:28am	220	138/76 L dn 3:15pm 141/79 R up 3:17pm	435
Tues, 11-15 No NO pills	127/85 L up 8:29pm 128/88 R dn 8:39pm	X	127/64 L dn 8:53pm 131/71 R up8:54pm	X
Wed, 11-16* Same arm	121/79 R dn 8:47am 117/87 R up 8:50am	X	146/80 L up 8:35am 132/64 L dn 8:38am	X
Thur, 11-17* No NO pills	111/72 R dn 6:35pm 115/87 L up 8:38pm	X	145/69 L dn 6:50pm 144/74 R up 6:59pm	X
Fri, 11-18* Same arm	122/78 Rdn10:02am 144/92 R up 1:25pm	X	140/82 L up 9:40am 123/78 L dn 9:38am	X
Sat, 11-19* Same arm	125/90 R dn 8:32am 119/89 R up 8:33am	X	123/69 L dn 8:36am 139/78 L up 8:42am	X
Sun, 11-20	138/95 R up 5:10pm 133/81 L dn 5:10pm	435	105/62 L dn 5:05pm 129/74 R up 5:08pm	435

Carol and Grant BP Record

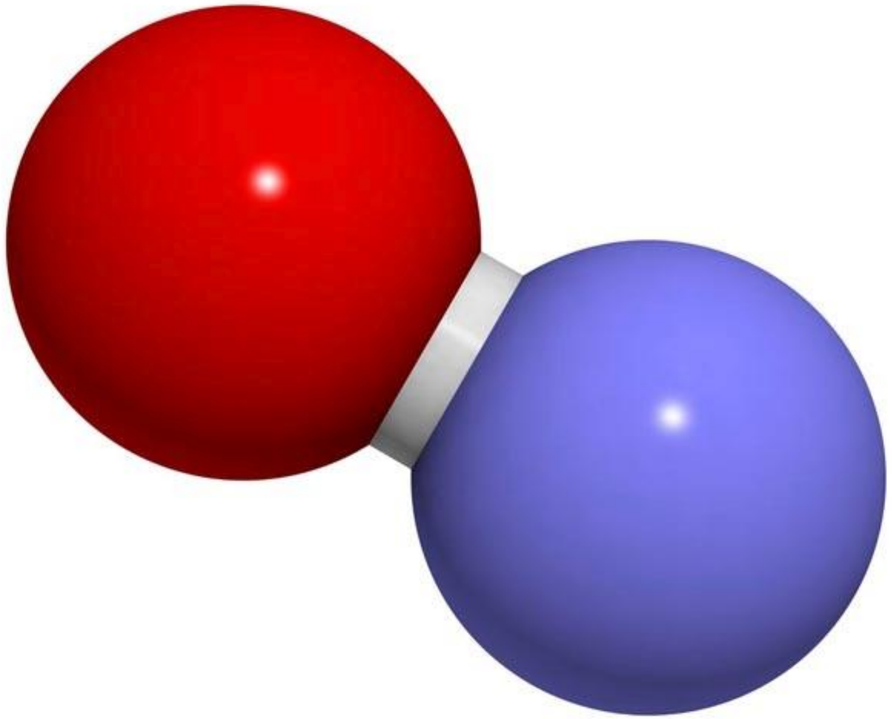
DATE	BP/Time	NO Result	BP/Time	NO Result
Mon, 11-21 Same arm	130/85 Ldn 12:31pm	X	127/63 R dn 12:48pm	X
Tues, 11-21 Same arm	122/83 Rdn 3:46pm 121/91 Rup 3:52pm	X	126/71 Ldn 7:52pm 136/71 Lup 8:04pm	X
Wed, 11-23 Same arm	135/86 Rdn 5:11pm 110/80 Rup 5:12pm	X	116/63 Ldn 5:05pm 139/65 Lup 5:08pm	X
Thur 11-24 Same arm	126/90 Ldn 8:27am 109/87 Lup 8:30pm	X	117/77 Ldn 9:39am 133/77 Lup 9:41am	X
Fri 11-25	SKIP		SKIP	
Sat 11-26 Same arm	129/82 Rdn 8:36am 127/88 Rup 8:38am	870	110/66 Rdn 9:49am 125/75 Rup 9:51am	220
Sun, 11-27 Same arm	129/83 Ldn 1:02pm 126/83 Lup 1:03pm	X	119/61 Ldn 1:48pm 144/77 Lup 1:51pm	X
Mon, 11-28 Same arm	119/76 Rup 8:22pm 102/76 Rup 8:25pm	X	127/71 Rdn 9:20pm 136/75 Rup 924pm	X
Tues, 11-29 Same arm	109/69 Lup 7:51pm 112/77 Ldn 7:53pm	X	151/84 Lup 9:47pm 141/70 Ldn 9:50pm	X

Ways to Increase *NO

- Eat nitrate rich foods => vegetables
- Exercise
- Reduce stress and oxidative burden
- Increase antioxidants
- Breathe…through the nose
- Support digestive enzymes esp HCL.
- Nitrate/Nitrite rich supplements
- Sauna, high temperature
- Avoid antiseptic mouthwash

*NO Supplementation

- Potassium Nitrate Beet Root Concentrate
- L- Arginine
- Citrulline
- Inhaled *NO gas



J PREV MED HYG 2022; 63(SUPPL. 3): E239-E245

Summary

- Nitric Oxide is an essential physiological “player” in every system of our body.
- Nitric oxide has a direct benefit on cognitive function, cardiovascular system, gastrointestinal system, exercise performance, metabolic syndrome and erectile function.
- Nitric oxide can be positively influenced by life-style factors.
- Dietary nitrates have a direct benefit on increasing systemic *NO and improving cognition.

Integrative Healthcare SYMPOSIUM

Thursday 1:30pm – 2:30pm

Nitric Oxide: The Ins and Outs of Its Clinical Significance

Please scan this QR code on you mobile
or tablet device to access the session feedback survey

Nitric Oxide: The Ins and Outs of Its C
linical Significance