Optimizing Nitric Oxide for Healthy Longevity

Feb 2024

Beth Shirley, RPh, CCN

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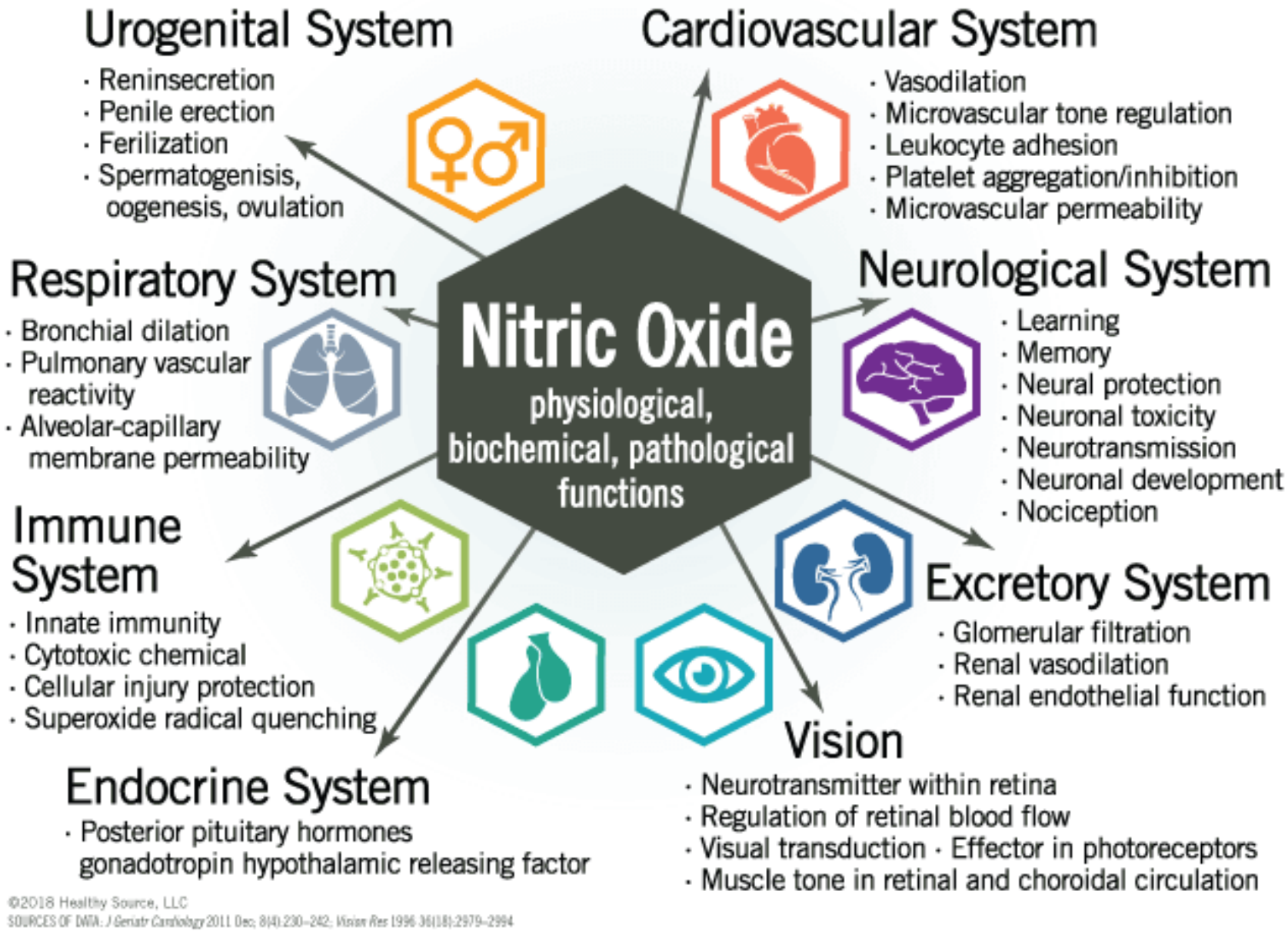
Beth developed an expertise as a pharmacist and certified clinical nutritionist during a 40+ year career. Her specialties include stress-induced hormonal imbalance, intestinal dysfunction, autoimmune and chronic inflammatory issues, detoxification, nutrigenomics and super-normal oxidative stress.

She has been a pioneer at the cutting edge of the evolution of what has now come to be known as “Integrative Pharmacy” - the junction between traditional pharmacy and the clinical use of nutritional supplementation.

Since 2009, Beth has spent time working with some of the leading thought leaders in the world of nitric oxide research and through this has developed an in-depth knowledge on the topic and its potential applications in patient care.

In addition, she has worked closely with the scientific community and cutting-edge companies working on innovative nutritional ingredients and approaches to their use for a variety of life’s challenges. In fact, Beth formulated a product that was awarded the first patent on a supplement to increase sexual desire and satisfaction.

Currently – Director of Education and Research - AMS


Urogenital System
· Reninsecretion
· Penile erection
· Ferilization
· Spermatogenisis, oogenesis, ovulation
Cardiovascular System
· Vasodilation
· Microvascular tone regulation
· Leukocyte adhesion
· Platelet aggregation/inhibition
· Microvascular permeability
Respiratory System
· Bronchial dilation
· Pulmonary vascular reactivity
· Alveolar-capillary membrane permeability
Nitric Oxide
physiological, biochemical, pathological functions
Neurological System
· Learning
· Memory
· Neural protection
· Neuronal toxicity
· Neurotransmission
· Neuronal development
· Nociception
Immune System
· Innate immunity
· Cytotoxic chemical
· Cellular injury protection
· Superoxide radical quenching
Excretory System
· Glomerular filtration
· Renal vasodilation
· Renal endothelial function
Endocrine System
· Posterior pituitary hormones gonadotropin hypothalamic releasing factor
Vision
· Neurotransmitter within retina
· Regulation of retinal blood flow
· Visual transduction · Effector in photoreceptors
· Muscle tone in retinal and choroidal circulation
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SOURCES OF DATA: J Geriatr Cardiology 2011 Dec; 8(4):230–242; Vision Res 1996 36(18):2979–2994

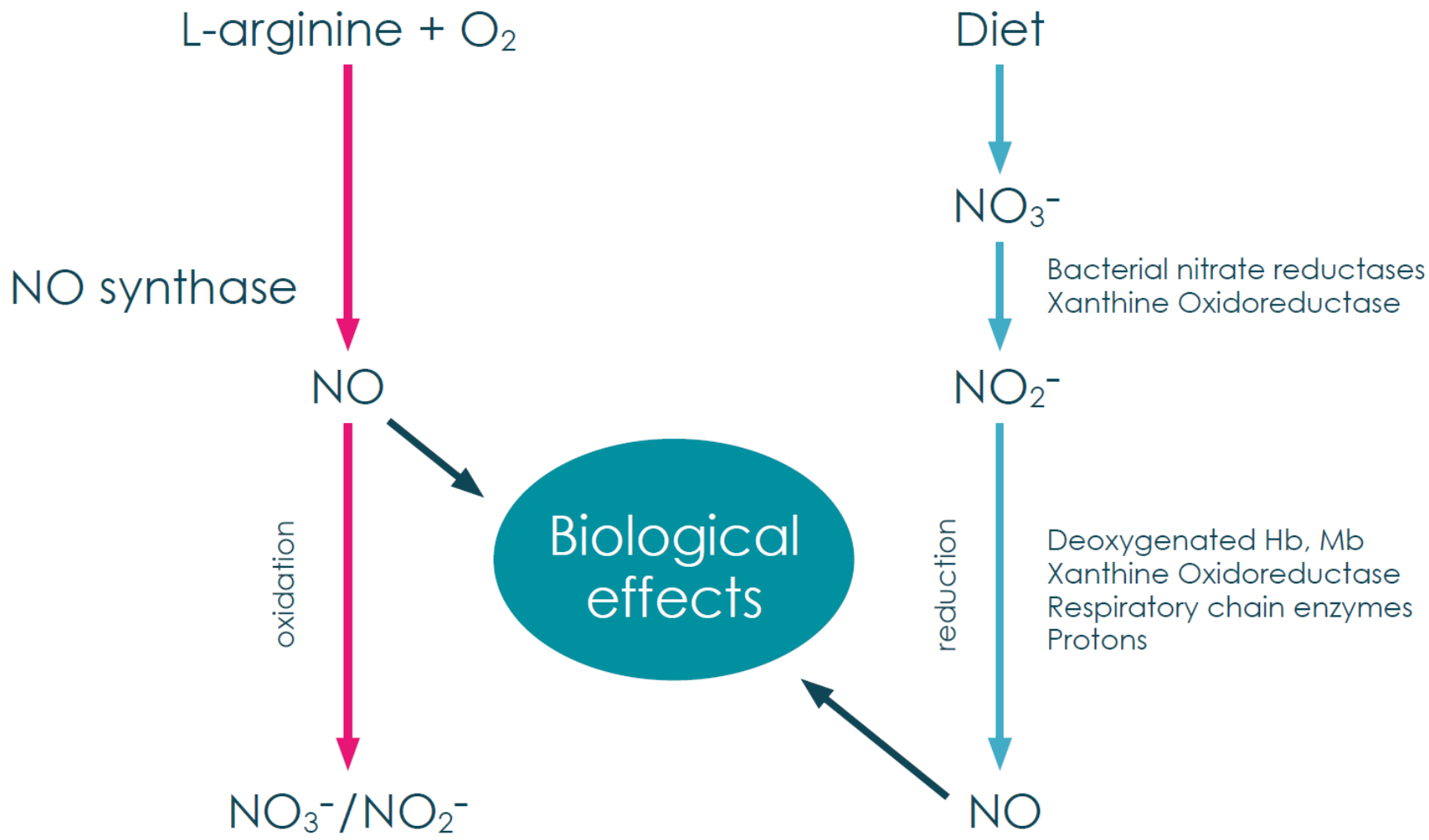
Why is NO Essential ?

- Regulates all CV function/homeostasis – circulation & microcirculation
- Red blood cells require adequate NO to deliver oxygen to cells
- Supports neurotransmitter function
- Regulates gastro-intestinal function including gastroparesis, mucus & microbiome
- Helps activate GLUT-4 receptor
- Essential for learning & memory
- Supports mitochondrial biogenesis
- Controls efficiency of mitochondria in generation of energy & generation of hormones
- Essential for sexual function – men & women
- Stem cell mobilization & differentiation
- Regulates immune system function
- Regulates inflammatory response & scavenges free radicals
- Modifies platelet activation/aggregation
- Supports telemorase activity

Pathways to Make NO

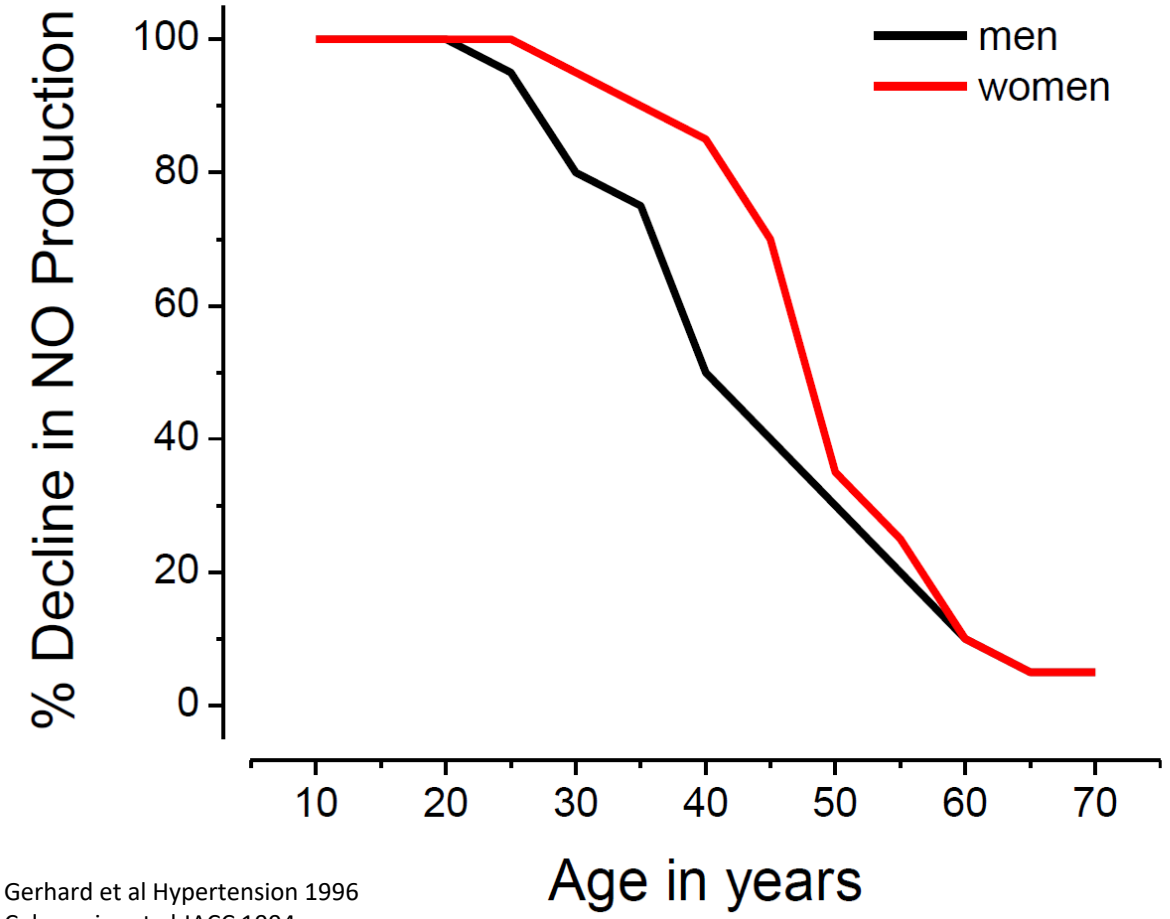
Arginine/NOS pathway

Nitrate/Nitrite/NO pathway



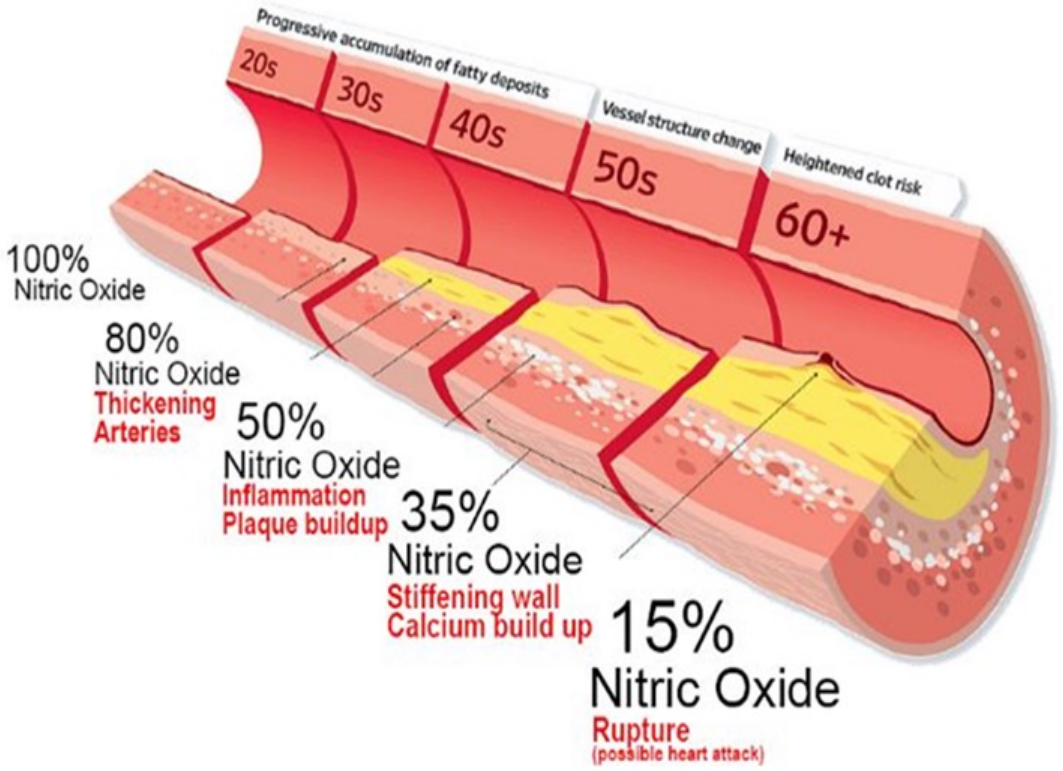
pH dependent
O2 dependent
FAD
FMN
NADPH
BH4
Fe

NO Production Decreases with Age



Gerhard et al Hypertension 1996
Celermajer et al JACC 1994
Taddei et al Hypertension 2001
Egashira et al Circulation 1993

Progression of Endothelial Dysfunction



Bryan NS Curr Atheroscler Rep. 2018 Mar 17;20(5):21

Factors Affecting NO Production

Supporting Nitrate/Nitrite/NO Pathways
Down-Regulates Superoxide Production & Oxidative Stress

3 main sources of Superoxide

1) **Uncoupled NOS** – nitrate increases BH4 production to recouple NOS
2) **NADPH oxidase (NOX)** – nitrate, nitrite and NO inhibit NOX
3) **Uncoupled mitochondrial ETC** – nitrite and NO recouple ETC

Oxidative stress & Inflammation - core of Every Single Chronic Health Issue

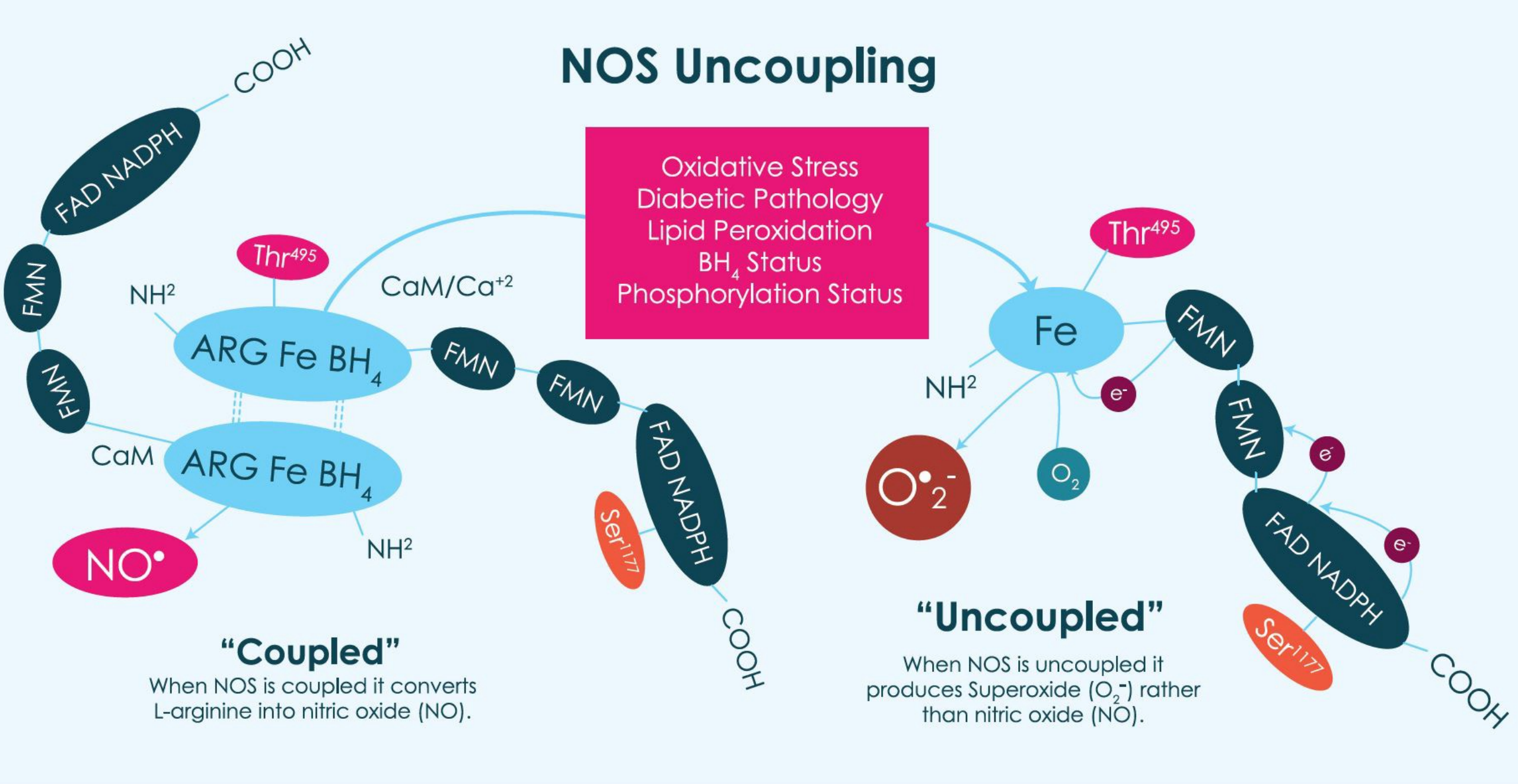
Kıvrak EG, Yurt KK, Kaplan AA, Alkan I, Altun G. Effects of electromagnetic fields exposure on the antioxidant defense system. J Microsc Ultrastruct. 2017 Oct-Dec;5(4):167-176. doi: 10.1016/j.jmau.2017.07.003 Epub 2017 Aug 2. PMID: 30023251; PMCID: PMC6025786.

Schuermann D, Mevissen M. Manmade Electromagnetic Fields and Oxidative Stress-Biological Effects and Consequences for Health. Int J Mol Sci. 2021 Apr 6;22(7):3772. doi: 10.3390/ijms22073772. PMID: 33917298; PMCID: PMC8038719.

Bryan, NS. (Winter 2019). Are you Nitric Oxide deficient?. Retrieved from https://www.allergyresearchgroup.blog/are-you-nitric-oxide-deficient-part-2-of-2/ on April 17th 2023

Kubes P, Wallace JL. Nitric oxide as a mediator of gastrointestinal mucosal injury?-Say it ain't so. Mediators of Inflammation. 1995 ;4(6):397-405. DOI: 10.1155/s0962935195000640. PMID: 18475671; PMCID: PMC2365665.

NOS Uncoupling



"Coupled"

When NOS is coupled it converts L-arginine into nitric oxide (NO).

"Uncoupled"

When NOS is uncoupled it produces Superoxide (O_2^-) rather than nitric oxide (NO).

NOS Uncoupling

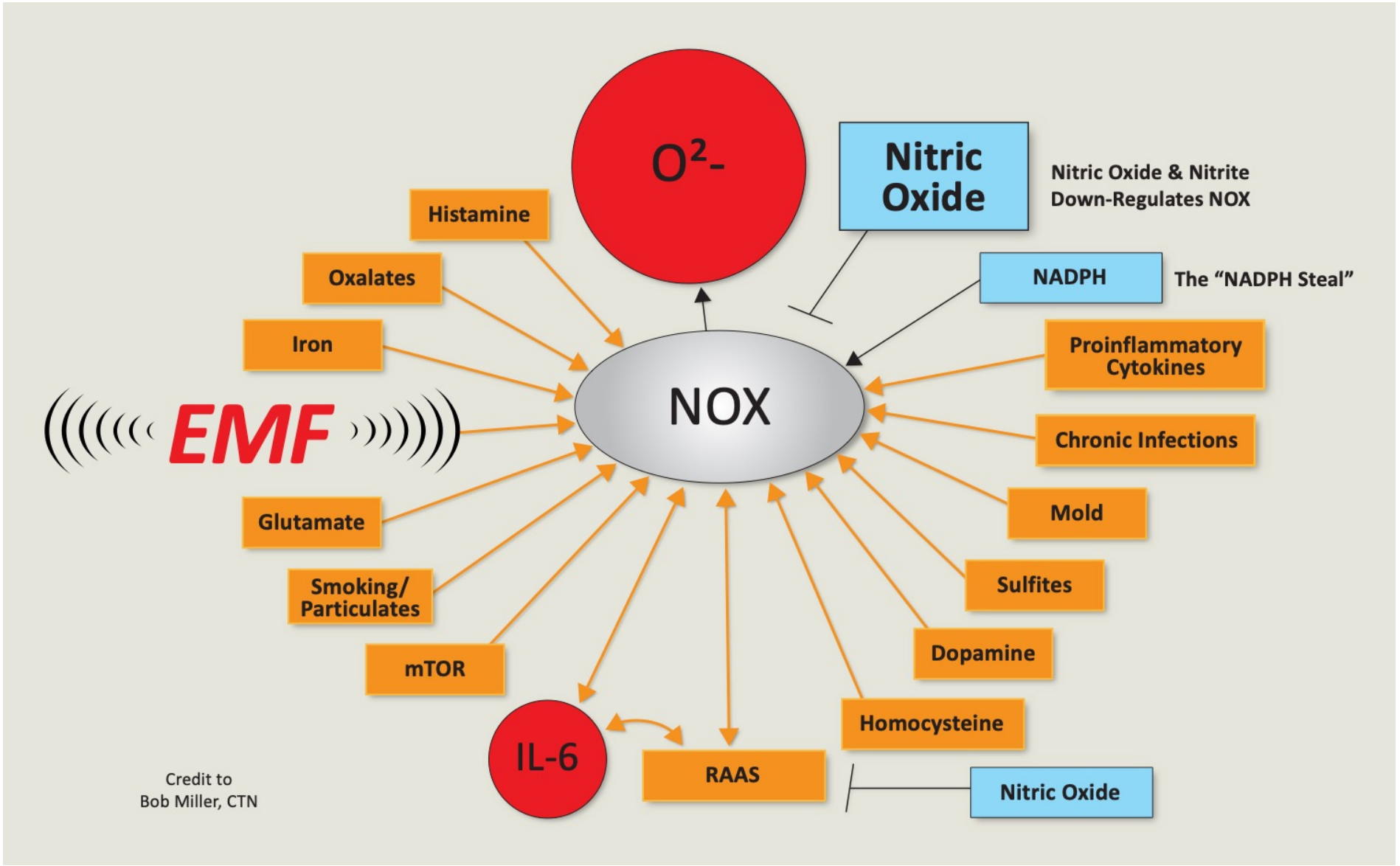
When NOS is uncoupled, it becomes a superoxide generator, not a NO producer

Rate limiting cofactor – BH4
Superoxide oxidizes BH4 to BH2
Other inhibitors- Aldosterone, Ang II, cortisol, oxidative stress
BH4 depleted, uncoupled NOS – Arginine stimulates superoxide increasing NOS uncoupling
Vitamin C – reduces BH3 back to BH4

Arginine is Not effective in aging population or anyone with any chronic health issue

Nitrate increases production of BH4 – BH4 recouples NOS

Alkaitis, M.S., Crabtree, M.J. Recoupling the Cardiac Nitric Oxide Synthases: Tetrahydrobiopterin Synthesis and Recycling. Curr Heart Fail Rep 9, 200–210 (2012). https://doi.org/10.1007/s11897-012-0097-5


O2-
Nitric Oxide
Nitric Oxide & Nitrite
Down-Regulates NOX
Histamine
Oxalates
Iron
EMF
NADPH
The "NADPH Steal"
Proinflammatory Cytokines
NOX
Chronic Infections
Mold
Glutamate
Smoking/ Particulates
Sulfites
Dopamine
mTOR
Homocysteine
IL-6
RAAS
Nitric Oxide
Credit to
Bob Miller, CTN

Increased Oxidative Stress Produced by Up-Regulated NADPH oxidase

Stimulates RAAS - Renin, Angiotensin 1, Ang 11, Aldosterone, IL6
Cardiometabolic disease – CVD, diabetes, IR
Impairs thyroid function
Inflames gut
Obesity
Impairs cognition
Impairs kidney function

Vicious cycle of inflammation – Every Where

Nitrite and NO down-regulate NAPDH oxidase

Mitochondria – make ATP and create voltage of cell

- Main source of intracellular O2 consumption & source of ROS
- ~2% of oxygen consumed not converted to H2O but to O2-

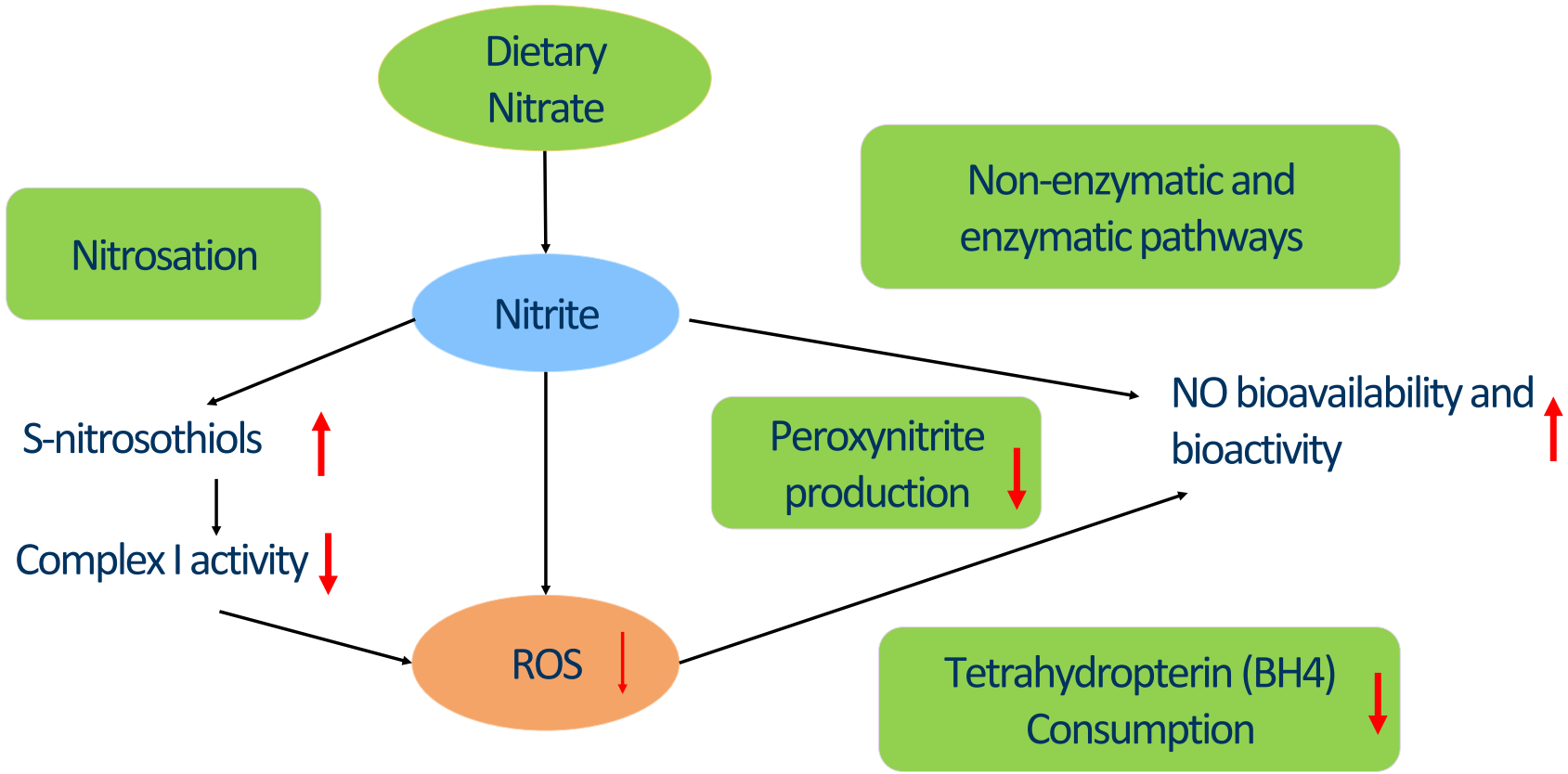
Mitochondria ETC reduce nitrite to NO in hypoxia – Complex I, III, IV (CCOX)

- Blood flow to cells more important than how much O2 carried by Hgb
- Does not always result in decreased ATP production

Nitrite and NO recouple ETC decreasing proton leak

Nitrite & NO stimulate hypoxic mitochondrial biogenesis by activating AMPK & SIRT 1 activating PCG1a

Sarti P, Magnifico MC, Altieri F, Mastronicola D, Arese M. New evidence for cross talk between melatonin and mitochondria mediated by a circadian-compatible interaction with nitric oxide. Int J Mol Sci. 2013 May 28;14(6):11259-76. doi: 10.3390/ijms140611259. PMID: 23759982; PMCID: PMC3709731.
Sruti Shiva, Nitrite: A physiological store of nitric oxide and modulator of mitochondrial function, Redox Biology, Volume 1, Issue 1, 2013, Pages 40-44, ISSN 2213-2317, https://doi.org/10.1016/j.redox.2012.11.005.



*Mechanisms of the protective effects of nitrate and nitrite in cardiovascular and metabolic diseases. Nitric Oxide. doi:10.1016/j.niox.2020.01.006

NO and immune competence

NO – essential in immune response

Defense against virus, bacteria, fungi and other pathogens

Regulates macrophages, T lymphocytes, antigen presenting cells, mast cells, neutrophils and NK cells

Immunoregulator

iNOS (NOS2) – part of immune response

eNOS (NOS3) – governs circulation and microcirculation

"Well vascularized tissues are more resistant to infections
And capable of localizing/containing offending agents.
By contrast, poorly vascularized tissues are relatively
Inefficient in responding to inflammatory stimuli"
~Dr Nathan Bryan

Major Beneficial Actions of NO on GI Tract

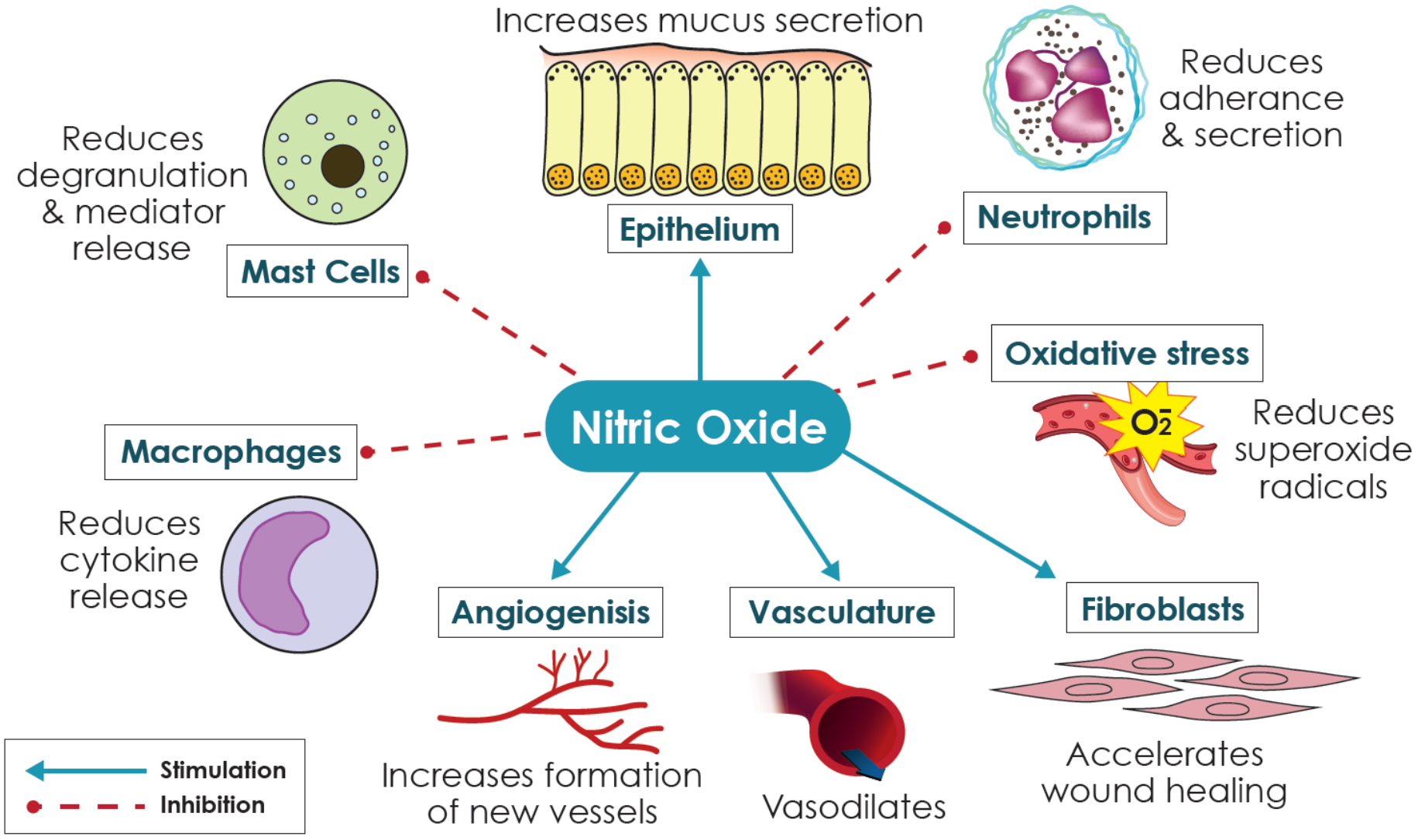


Diagram: Magierowski, M.; Magierowska, K.; Kwiecien, S.; Brzozowski, T. Gaseous Mediators Nitric Oxide and Hydrogen Sulfide in the Mechanism of Gastrointestinal Integrity, Protection and Ulcer Healing. *Molecules* 2015, 20, 9099-9123.

Supporting Nitrate/Nitrite/NO Pathway Supports Healthy GI Tract

Nitrate:

Decreases levels of bacteria associated with poor systemic health

Protects gut microbiome under inflammatory conditions

Prevents or reduces dysbiosis

Stimulates eubiosis

All microbiomes are connected

Nitrate protects microbiome and increases microbial biomass

Nitrate protects and restores tight junction proteins and repairs leaky gut

Microbiota and human reproduction: the case of female infertility. doi:10.3390/ht9020012
Gaseous meditators nitric oxide and hydrogen sulfide in the mechanism of gastrointestinal integrity, protection and ulcer healing. doi.org/10.3390/molecules20059099
Nitrate from diet might fuel gut microbiota metabolism: minding the gap between redox signaling and inter-kingdom communication. Doi.org/10.1016/j. freeradbiomed.2020.02.001

Nitrate, NO and Intestinal Barrier Proteins

Tight junction proteins

- Important in epithelial transport
- Responsible for barrier integrity of intestinal tract
- Found in intestinal tract, BBB, kidney, skin, bile duct, lung

Loss of tight junction proteins cause a breakdown of the barrier and leaky gut, leaky brain

Dysbiosis: decreased gastric expression of tight junction proteins occludin and claudin 5

Nitrate consumption supports the rebound in levels of occludin and claudin 5

BDNF

- Homeostatic regulation of intestinal barrier integrity
- Affects expression of tight junction proteins
- Decreased BDNF increases IBS
- Also has role in depression, anxiety, learning and memory

NO essential mediator of BDNF

Microbiota and human reproduction: the case of female infertility. doi:10.3390/ht9020012
Gaseous meditators nitric oxide and hydrogen sulfide in the mechanism of gastrointestinal integrity, protection and ulcer healing. doi.org/10.3390/molecules20059099
Nitrate from diet might fuel gut microbiota metabolism: minding the gap between redox signaling and inter-kingdom communication. Doi.org/10.1016/j. freeradbiomed.2020.02.001

Mast cells– Effectors of Gut-Brain-Immune Axis

Mast cells line all mucus membranes

- Release histamine, cytokines, chemokines, interleukins, PAF
- Activated by superoxide
- Activated in absence of NO

Translate environmental stress signals

- Release neurotransmitters & pro inflammatory cytokines

Nitrites and NO regulate activity of mast cell

- Inhibit mast cell dependent inflammatory events
- Suppress antigen-induced degranulation
- Suppress mediator release including histamine and cytokines
- Inhibit leukocyte endothelial cell attachment
- Inhibit generation of ROS by mast cells

Nitrates Play a Significant Role in Protecting GI Health

Inhibit inflammatory process
Down-regulate oxidative stress
Scavenge free radicals
Downregulate an up-regulated iNOS
Powerful modulator of microbiome
Prevent dysbiosis
Prevent and repairs leaky gut
Promotes healthy gut-brain-immune axis
Modulate immune and oncological pathways
Maintain homeostasis

Mediators between oral dysbiosis and cardiovascular diseases

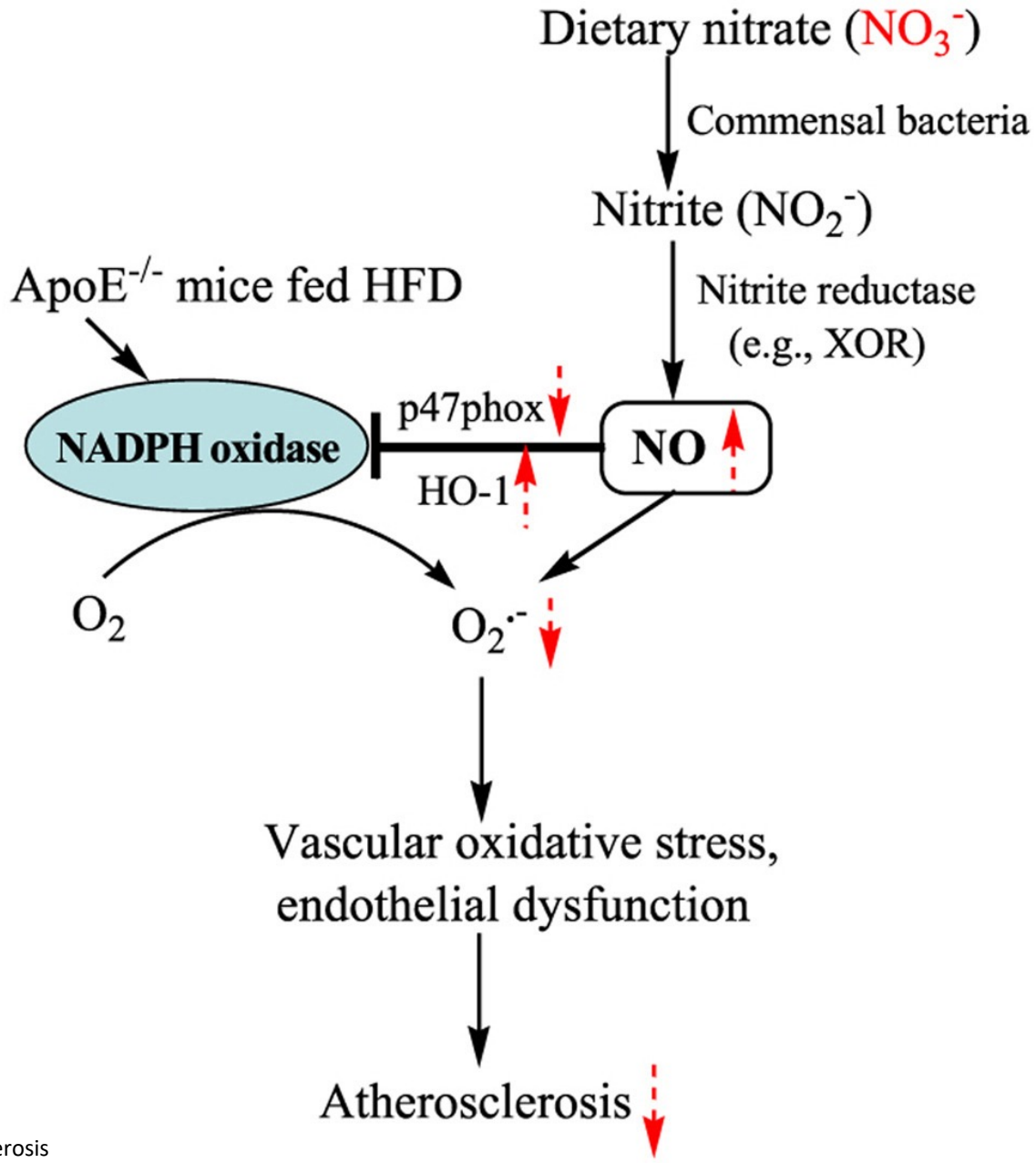
Sept 2018 doi.org/10.1111/eos.12423

Clinical periodontitis - increased risk for cardiovascular diseases
through systemic inflammation
Exposed to bacteria and their by-products
Access to circulation directly through inflamed oral tissues
Indirectly (via saliva) through GI tract
Systemic inflammatory and immunologic responses

Oral dysbiosis -increased risk for subclinical atherosclerosis
Prevalent and future **coronary artery disease**
Incident and recurrent **stroke**

Dietary nitrate attenuated endothelial dysfunction and atherosclerosis in apolipoprotein E knockout mice fed a high-fat diet: A critical role for NADPH oxidase

Nitrate/Nitrite/NO
Inhibits NADPH oxidase
Decreases oxidative stress
Decreases endothelial dysfunction
Protects against atherosclerosis



Rou Peng, Mengjuan Luo, Rong Tian, Naihao Lu, Dietary nitrate attenuated endothelial dysfunction and atherosclerosis in apolipoprotein E knockout mice fed a high-fat diet: A critical role for NADPH oxidase, Archives of Biochemistry and Biophysics, Volume 689, 2020, 108453, ISSN 0003-9861, https://doi.org/10.1016/j.abb.2020.108453.

NO, Circulation, Microcirculation

Vasodilation and blood flow
Anti-atherogenic - inhibits vascular plaque
Anti-thrombotic – inhibits activation and aggregation
Controls endothelial permeability
Inhibits adhesion molecule activation/expression in endothelium
Inhibits leukocyte adherence and migration into endothelium
Inhibits arterial stiffness
Inhibits inflammation

Impaired circulation and microcirculation – healing can not and will not happen

NO & Diabetes

70% of diabetics develop DPN within 5 years

- Impaired blood flow
- NO is a neurotransmitter in some autonomic fibers

Arginine/NOS pathway impaired in diabetes

- NOS pathway is pH dependent
- Diabetes decreases pH to more acidic state
- NOS requires oxygen – circulation is impaired so less O2 delivered
- Diabetes increases ADMA – inhibits NOS
- Rampant oxidative stress in diabetes – oxidative stress uncouples NOS

Insulin resistance

- increases NOS uncoupling
- Loss of endothelial function
- Increased adhesion molecule formation (VCAM 1)
- Increased oxidative stress

GLUT 4 receptor requires adequate NO

HbA1c binds tightly with NO – making NO not bio-available

Nitric oxide, peripheral neuropathy and diabetes doi:10.1007/978-1-4612-1328-4.14
Adapting the stress response: viral subversion of the mTOR signaling pathway DOI:10.3390/v8060152

Modulation of mitochondria and NADPH oxidase function by the nitrate-nitrite-NO pathway in metabolic disease with focus on type 2 diabetes

Aug 2020 doi.org/10.1016/j.bbadis.2020.165811

Dietary nitrate reverses metabolic syndrome

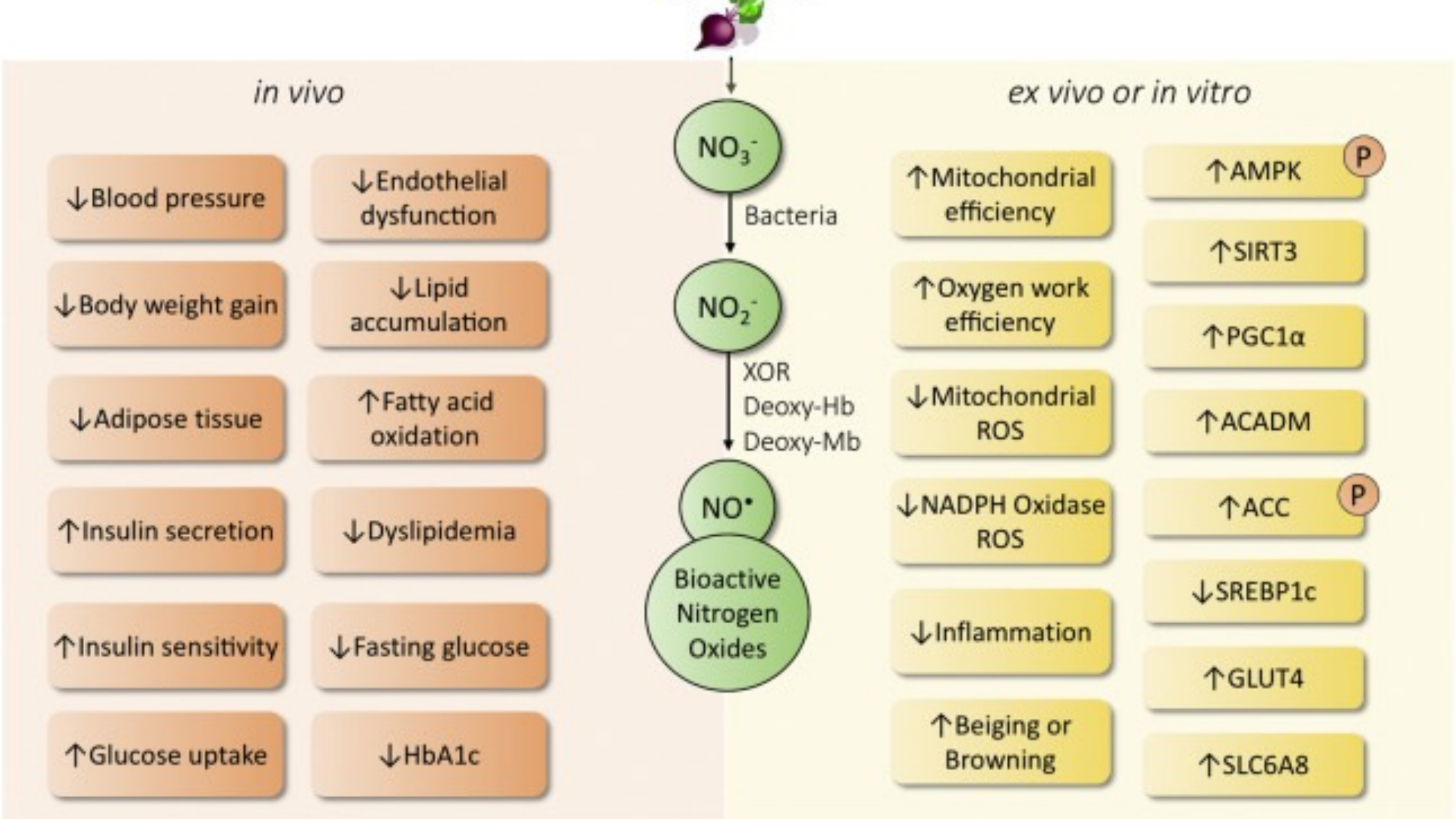
- Lowering bp
- Restore glucose/insulin homeostasis
- Reduce fat accumulation

Protective effects of nitrate supplementation in obesity, Met S and T2D

Induces expression of brown adipose tissue (BAT) specific genes – antidiabetic effects

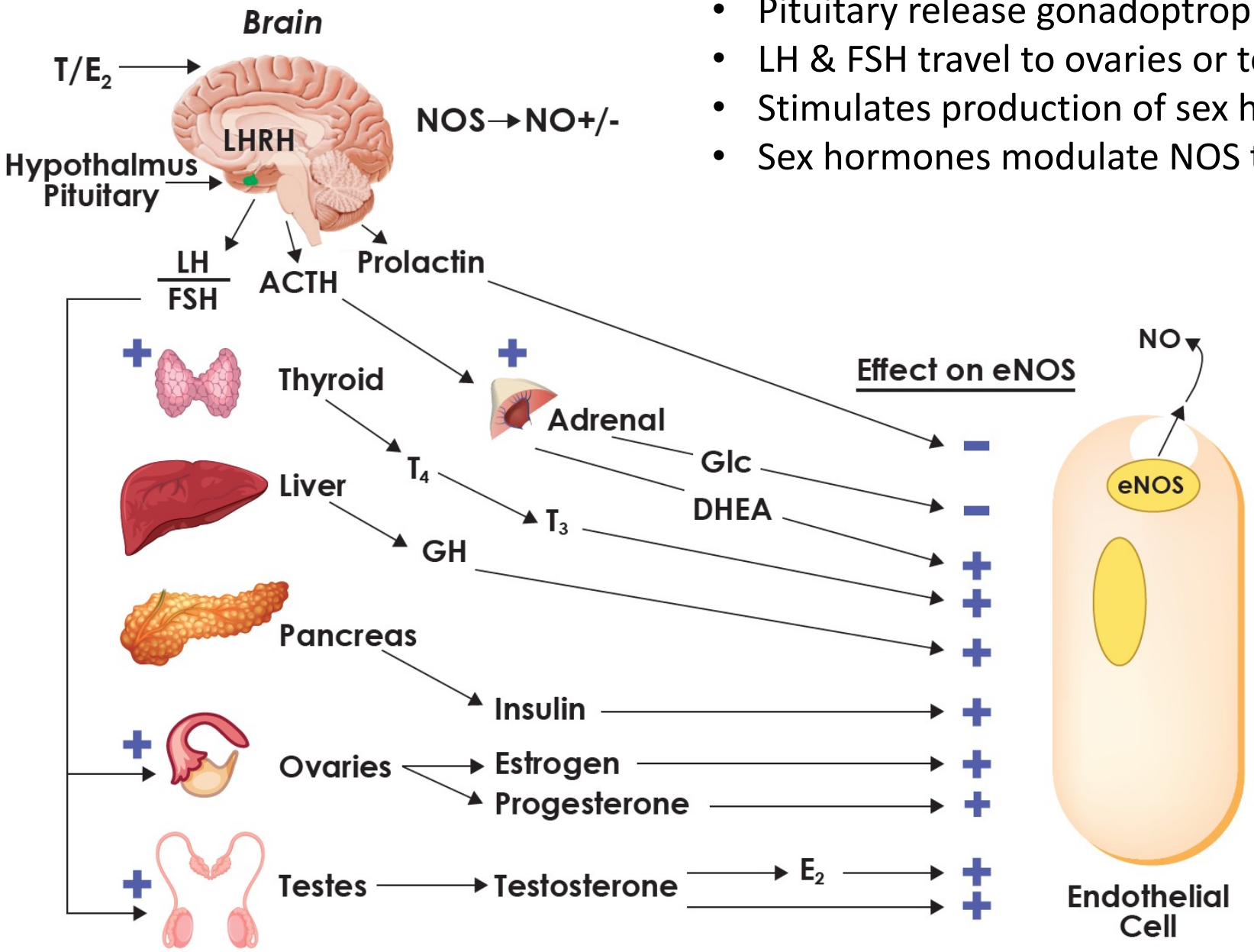
Nitrate/Nitrite on mitochondrial functions

- Browning of white adipose tissue
- PGC-1α and SIRT3 dependent AMPK activation
- GLUT4 translocation
- Mitochondrial fusion-dependent improvements in glucose homeostasis
- Dampening of NADPH oxidase activity


in vivo
↓Blood pressure
↓Endothelial dysfunction
↓Body weight gain
↓Lipid accumulation
↓Adipose tissue
↑Fatty acid oxidation
↑Insulin secretion
↓Dyslipidemia
↑Insulin sensitivity
↓Fasting glucose
↑Glucose uptake
↓HbA1c
NO_3^-
Bacteria
NO_2^-
XOR
Deoxy-Hb
Deoxy-Mb
NO•
Bioactive Nitrogen Oxides
ex vivo or in vitro
↑Mitochondrial efficiency
↑Oxygen work efficiency
↓Mitochondrial ROS
↓NADPH Oxidase ROS
↓Inflammation
↑Beiging or Browning
↑AMPK
P
↑SIRT3
↑PGC1α
↑ACADM
↑ACC
P
↓SREBP1c
↑GLUT4
↑SLC6A8

NO & Hormones

- Regulates hypothalamic release of GnRH/LHRH
- Pituitary release gonadoptropins LH & FSH
- LH & FSH travel to ovaries or testis
- Stimulates production of sex hormones
- Sex hormones modulate NOS to increase NO



Stress, Glucocorticoids, NO deficiency

Glucocorticoids inhibit NO production

- Increase ROS in mitochondria, NADPH oxidase, xanthine oxidase
- Oxidative stress uncouples NOS
- Alters flora/increases dysbiosis
- Decreases synthesis of BH4
- Decreases membrane transport of arginine
- Increases blood glucose increasing oxidative stress
- Increases HgbA1C – binds tightly with NO

Stress induces an inflammatory response and damage to all cells including gut

Increases dysbiosis and leaky gut

Optimizing nitrate/nitrite/NO pathway protects GI tract

Hormonal modulation of endothelial nitric oxide production. doi: 10.1007/s00424–010–0797–1
Nitric oxide, peripheral neuropathy and diabetes. Doi:10.1007/978–1–4612–1328–4_14
Nitrate ameliorates DSS-induce colitis by regulating the homeostasis of the intestinal microbiota. Doi. org/10.1016/j.freeradbiomed.2019.12.002

PCOS and NO Deficiency

Most common endocrine disorder in reproduction women

Up to 20%

2/3 of those not ovulating on regular basis causing infertility

With age, PCOS morphs into a metabolic disease:

Insulin resistance

Impaired glucose tolerance

T2D

Dyslipidemia

Hypertension

Cardiovascular disease

All mediated by NO

BC pills – allopathics answer uncouples NOS

Characteristics of PCOS throughout life. Doi:10.1177/2633494120911038
Oxidative stress and cardiovascular complications in PCOS. Doi:10.1016/ejogrb.2015.05.005

NO & Fertility

Latest WHO data 1 in 6 have trouble getting &/or staying pregnant

Oxidative stress – primary cause of infertility in male and females

Toxins, environmental poisons in air, water, food

NO affects all stages & functions of reproductive process in both males & females

NO donors may be useful for promoting fertility

NO inhibitors shown to be useful for contraception

Many key infertility drivers have NO deficiency at their base

Cardiovascular concerns with improper blood flow

Metabolic and blood glucose/insulin issues

Polycystic ovary syndrome (PCOS)

Intestinal health issues

Immune and autoimmune issues

Mitochondrial health issues

EMF exposures

Stress

World Health Organization. WHO who.net April 3, 2023

he effects of oxidative stress on female reproduction: a review. doi:10.1186/1477-7827-10-49

Nitric Oxide and its role during pregnancy: from ovulation to delivery doi:10.2174/1381612033391784 2003

NO & Cognition

High bp - risk factor for cognitive decline & dementia
50% of adults have high bp
Hypertension occurs decades prior to onset of dementia, affecting blood flow in body as well as brain
Brain - 2% of our body mass yet consumes 25% of body's requirement for oxygen
Brain produces 20X more NO than entire vasculature

NO governs circulation and microcirculation
Impairment of blood flow to brain increases risk of neurodegenerative diseases
NO in hypothalamus and cerebral cortex - learning process and memory formation
Neuromodulator
Synaptic plasticity/BDNF
Neurogenesis – NSC
Mitochondrial function and biogenesis

Optimal NO Essential for Healthy Cognition

Hemoglobin requires NO attached to release oxygen to cells & tissues
Without adequate NO, **oxygen delivery impaired**

Brain – 2% of body mass
Consumes 20% of body's requirement for oxygen

Oxygen deficient – hypoxia
- Decreased ATP production aka decreased energy
- Mito become uncoupled
- Superoxide production increased

Cytochrome C oxidase becomes nitrite reductase enzyme
- Slows down oxygen consumption
- Increase NO production
- Improves microcirculation

Raichle ME, Gusnard DA. Appraising the brain's energy budget. Proc Natl Acad Sci U S A. 2002 Aug 6;99(16):10237-9.
doi: 10.1073/pnas.172399499. Epub 2002 Jul 29. PMID: 12149485; PMCID: PMC124895

Endophenotype-based in silico network medicine discovery combined with insurance record data mining identifies sildenafil as a candidate drug for Alzheimer's disease - *Dec* 2021 doi: 10.1038/s43587-021-00138-z

7.23 million people, sildenafil associated with 69% reduced risk of Alz
Increased neurite growth
Decreased tau expression in neuron

PDE5 inhibitors prolong action of cGMP to allow NO to hang around longer
Must have adequate NO in order for them to work
Alz - impaired neurotransmission, increased oxidative stress, reduced cerebral blood flow (CBF) or neuroinflammation

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

Jan 2011 https://doi.org/10.1016/j.niox.2010.10.002

Chronic ischemia in white matter associated with aging
Leading to cognitive decline and dementia
Frontal regions particularly compromised by aging
Decline in executive function

Nitrate beneficial for compensating for endothelial dysfunction
Nitrate increased cerebral blood flow within subcortical and deep white matter of frontal lobes involved with executive functioning

AMP-activated protein kinase activation and NADPH oxidase inhibition by inorganic nitrate and nitrite prevent liver steatosis

Dec 2018 doi.org/10.1073/pnas.1809406115

Fatty liver affects up to 25% in US with over half diagnosed with T2D

Positive correlation between lipid accumulation and up-regulated NADPH oxidase
Nitrate/nitrite/NO – inhibits NADPH oxidase production of superoxide & oxidative stress
Stimulates AMPK - master regulator of cellular metabolism and energy homeostasis
- regulates lipogenesis
- fatty acid oxidation
- glucose homeostasis

Effects of nitrite seen at levels achieved after ingestion of nitrate-rich vegetables
Nitrate and nitrite potently protected against diet-induced liver steatosis in vivo

Dietary nitrate supplementation could be useful in prevention and treatment of T2D and its complications such as NAFLD

Factors Affecting Sexual Response

Age

Decreased BH4 production

Uncoupled NOS increasing superoxide and oxidative stress

Diabetes/Blood Sugar Dysregulation

Develop ED 10-15 years earlier

Increased arginase II downregulating NO production

Increased ADMA

Alcohol - Acetaldehyde increases oxidative stress uncoupling NOS

Smoking

Increased oxidative stress

Impairment arginine/NOS pathway

Oral dysbiosis affecting nitrate/nitrite/NO pathway

STRESS….

ED = ED

Erectile Dysfunction = Endothelial Dysfunction

Testosterone – dual action:

1) Modulates NO/cGMP signaling mechanism by upregulating NOS
2) Modulates PDE5 activity regulating homeostatic mechanisms of erection

PDE5 Inhibitors prolong the action of cGMP to extend erections

THEY DO NOT CAUSE ERECTIONS

Adequate NO required for PDE5 Inhibitors to work.

Not effective in almost 50% of men treated

CAUTION on use of aromatase inhibitors (anastrozole, letrozole) and DHT blockers/5 alpha reductase inhibitors. Both of these may decrease production of NO and increase occurrence of ED and CV complications

NO Modulates Female Sexual Response

Potent vasodilator of clitoral, labial and vaginal tissue

NANC neurotransmitter relaxes smooth muscles, increases blood flow & response

Increased blood flow means better orgasms

Neurotransmitter modulating release of oxytocin and LHRH – sexual behavior

Oxytocin (cuddle/love hormone) increases NO and orgasms increase oxytocin

Involved in creation of long-term memory

Studies show that memory & libido closely connected

Following sexual stimulation, NO modulates release 3-5ml vaginal transudate

SSRIs inhibit NOS, decreasing NO blocking arousal in both men and women

Leads to problems with desire, arousal, orgasm and ejaculation in men

Sleep & the Circadian Rhythm

Impaired NO production – phase shift of circadian clock and disturbed sleep
nNOS production of NO in neurons of brain signal sleep and sleep patterns
Regulation of REM sleep age-dependent process involving NO

Sleep disorders risk factors for cardiometabolic conditions including obesity, hypertension, stroke, coronary heart disease, heart failure

Obstructive Sleep Apnea (OSA) – Hypoxic, NO deficiency state
- Increased oxidative stress
- Stimulates NADPH oxidase
- Uncoupled NOS
- Increased ADMA (linked to increase in all cause mortality)

Supporting nitrate/nitrite/NO pathway
- Decreases oxidative stress
- Recouples NOS
- Decreases ADMA

NO Involved in regulation of anxiety

Anxiety & depression **-** low levels of BDNF

Mediates neuroprotective actions of BDNF

Promotes neuronal survival

Stimulating neurogenesis

Enhances learning and memory

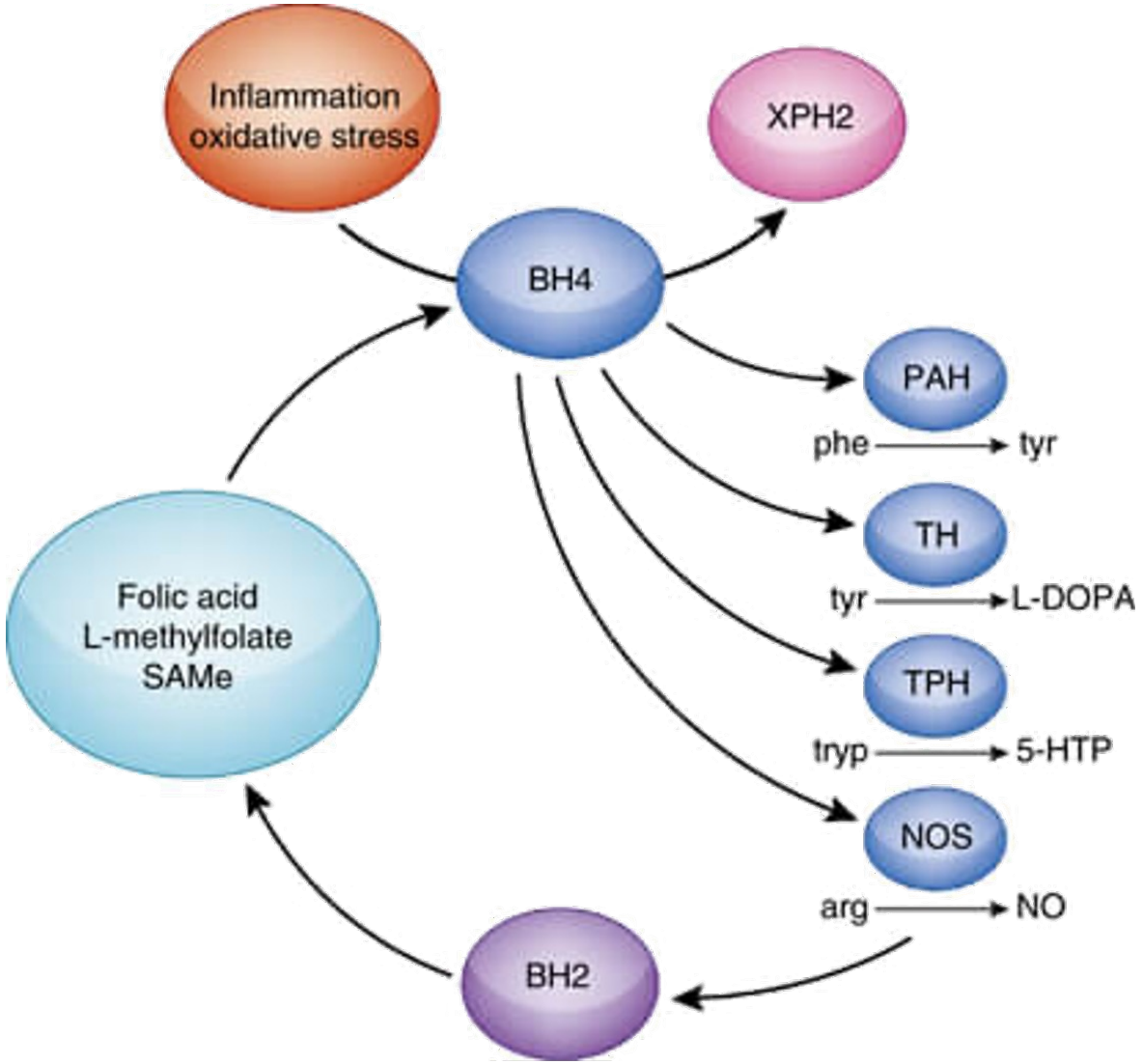
Role in synaptic plasticity which positively influences mood

Increases GABA in the brain

Nitrates increase production of BH4

increasing the production of neurotransmitters

BH4s Role in CV & Cognitive Health



Effects of a Short-Term High-Nitrate Diet on Exercise Performance

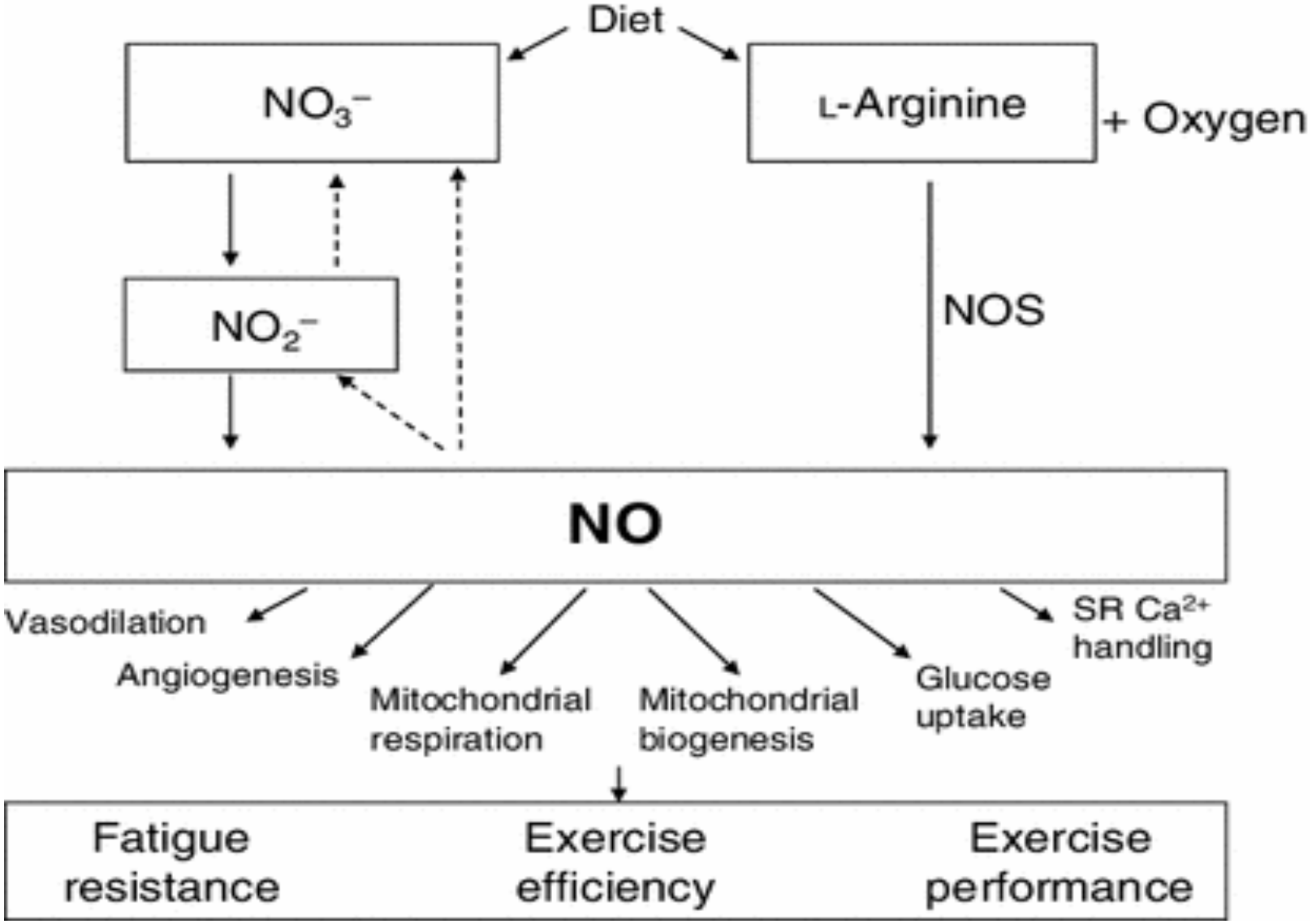
Nutrients. **2016 Sep**; 8(9): 534 doi: 10.3390/nu8090534

Reduces oxygen cost during moderate-intensity exercise
Improves exercise tolerance
Feasible strategy for increasing plasma nitrate/nitrite levels

Improves moderate intensity aerobic or high-intensity intermittent performance

Dietary nitrate supplementation and exercise performance

Sports Med **2014 May**;44 Suppl 1(Suppl 1):S35-45. doi: 10.1007/s40279-014-0149-y



EMF Increases Superoxide and Oxidative Stress

Uncouples NOS
Activates NADPH oxidase (NOX)
Uncouples mitochondrial ETC
Increases activity of MPO increasing H2O2
Stimulates XO increasing superoxide
Stimulates Fenton Reaction – increased HFE SNPs in English, Irish, Ashkenazi
Increases intracellular influx of Ca2+ simulating NADPH oxidase

NO inhibits VGCC influx of Ca2+
NO, as an endogenous mitochondrial K-ATP channel opener
Recouples mitochondria optimally blunting mitochondrial Ca2+ overload without undermining ATP synthesis
Supporting nitrate/nitrite/NO pathway addresses
Every Single one of these factors to decrease oxidative stress

Manmade electromagnetic fields and oxidative stress – biological effects and consequences for health doi:10.3390/ijms22073772
Modulation of voltage-gated Ca2+ current in vestibular hair cells by nitric oxide doi:10.1152/jn.00849.2006
Activation of mitochondrial ATP-dependent potassium channels by nitric oxide doi.org/10.1161/01.CIR.101.4.439
Modulation of CaV1 and CaV2.2 channels induces by nitric oxide via cGMP-dependent protein kinase doi:10.1016/j.neuint.2004.03.019

EMF Impairs NO production

EMF classified as immunosuppressant

NO – essential for defense against pathogens

Causes biological stress response – downregulates NO

Long term stress (EMF exposure) dysregulates immune response

80% of immune system in gut

Alters gut-brain-immune axis – destroys BBB

Increased Ca2+ influx – significantly increased cytokine storms

Increases HbA1C, T2D, CVD

Stimulates NADPH oxidase increasing superoxide production

Oxidative stress down-regulates NO production

Manmade electromagnetic fields and oxidative stress – biological effects and consequences for health doi:10.3390/ijms22073772
Modulation of voltage-gated Ca2+ current in vestibular hair cells by nitric oxide doi:10.1152/jn.00849.2006
Dirty electricity elevates blood sugar among electrically sensitive diabetes and may explain brittle diabetes doi.org/10.1080/15368470802072075
Effects of exposure to electromagnetic field radiation generated by activated mobile phones on fasting blood glucose doi:10.2478/s13382-013-0107-1

Supporting Nitrate/Nitrite/NO pathway during inflammation

Blocks cytokine storm
Down-regulates inflammatory cytokines – NLRP3, IL1B, IL6, IL18
Decreases mast cell degranulation – release of histamine
Decreases myeloperoxidase activity – H2O2
Stops hypoxia/reperfusion injury
Limit lipid peroxidation
Decrease IL17 decreasing inflammation
Rebalance T cells

- Decrease proinflammatory TH1 and TH17
- Increase T reg cells – maintain homeostasis and self tolerance

Restores oxygen, nutrient & glucose delivery and cellular waste removal

NO & Stem Cells

Repair system for the body and are required for ALL healing
Unprogrammed, unspecialized, master cells in body
Potential to develop into other types of specialized cells

NO is essential for:

- Stem cell viability
- Regulating stem cell differentiation
- Stimulating proliferation
- Supporting migration

Repair of damaged cells – essential to healthy longevity

HBOT increases NO affecting certain enzymes in bone marrow, stimulating release of stem cells from bone marrow

Nitric Oxide and Endothelial Cellular Senescence

NO activates telomerase and delays endothelial cell senescence
Prevents down regulation of telomerase activity
Delays senescence

Shortening of telomeres not strictly function of number of cellular divisions…
Telomeres can be modulated

Limana F, Capogrossi MC, Germani A. The epicardium in cardiac repair: from the stem cell view. Pharmacol Ther. 2011 Jan;129(1):82-96. doi: 10.1016/j.pharmthera.2010.09.002. Epub 2010 Oct 19. PMID: 20937304.
Vasa M, Breitschopf K, Zeiher AM, Dimmeler S. Nitric oxide activates telomerase and delays endothelial cell senescence. Circ Res. 2000 Sep 29;87(7):540-2. doi: 10.1161/01.res.87.7.540. PMID: 11009557.

Nitric Oxide and Endothelial Cellular Senescence

Nitric Oxide:

- Decreases ROS production
- Scavenges ROS
- Inhibits NADPH oxidase

Increased Nitric Oxide bioavailability:

- **Activates telomerase**
- **Inhibits cellular aging**
- **Delays cellular senescence**

Limana F, Capogrossi MC, Germani A. The epicardium in cardiac repair: from the stem cell view. Pharmacol Ther. 2011 Jan;129(1):82-96. doi: 10.1016/j.pharmthera.2010.09.002. Epub 2010 Oct 19. PMID: 20937304.
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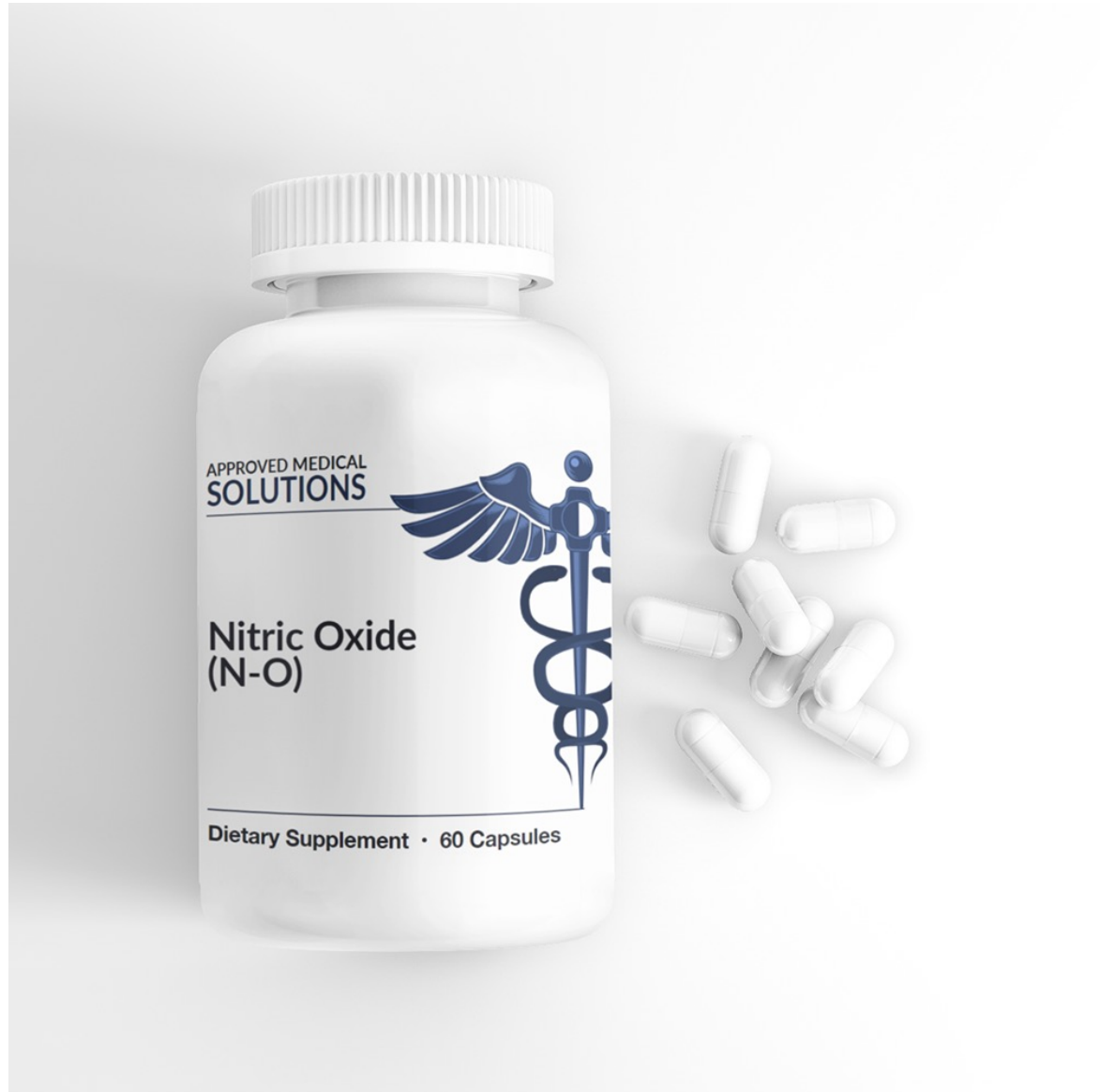
Perfect Storm for Impaired NO Production

Age – especially over 40
Physical inactivity
SAD Diet – inflammatory
Antibiotics
Antifungals - azole
Antidepressants - SSRI
BC pills
NSAIDs/COX2 inhibitors
PPIs

Achlorhydria
Antiseptic mouthwash
Fluoride and whitening toothpaste
Glyphosate – depletion of BH4
Pollution
EMF
Stress


APPROVED MEDICAL
SOLUTIONS
Nitric Oxide
(N-O)
Dietary Supplement • 60 Capsules

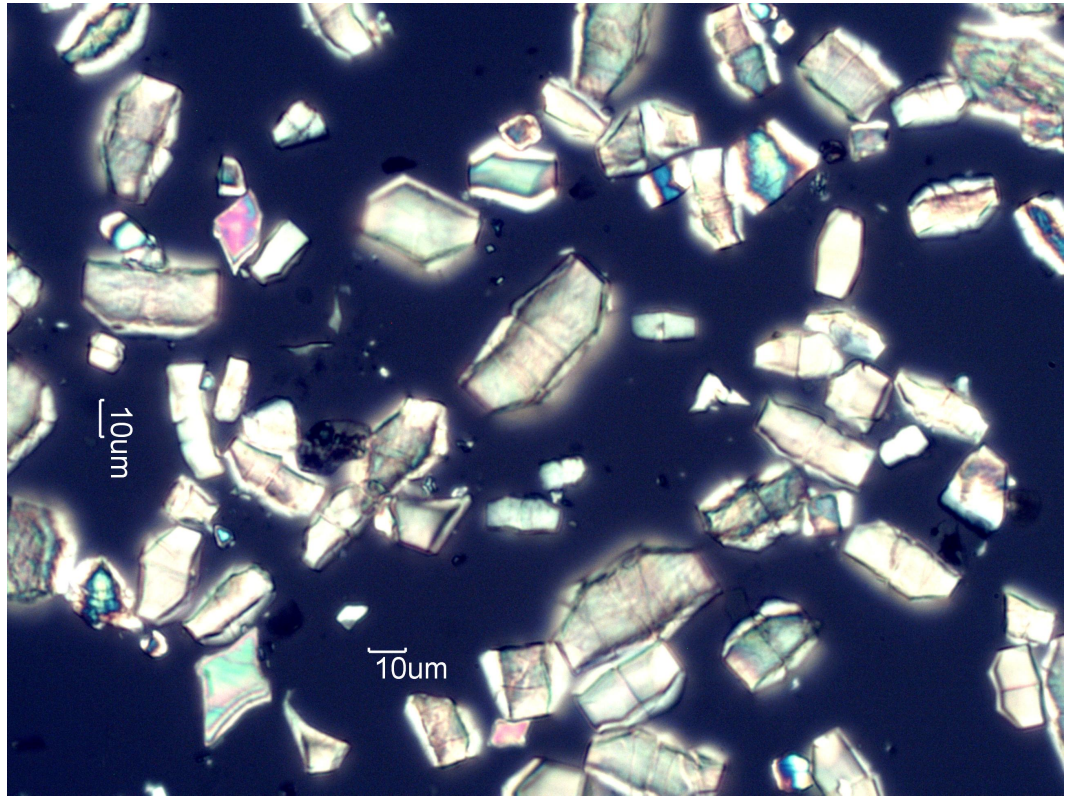
Supplement Facts

Serving Size 2 Capsules — Servings Per Container 30

	Amount Per Serving	% DV
Vitamin C (as Magnesium Ascorbate)	270 mg	300%
Thiamin (Thiamin Mononitrate)	60 mg	5000%
Folate (as L5-MTHF (Methyltetrahydrofolate))	100 mcg DFE	25%
Vitamin B12 (as Methylcobalamin)	50 mcg	2083%
Magnesium (as Magnesium Ascorbate)	84 mg	20%
Zinc (as Zinc Citrate)	5 mg	45%
Copper (as Copper Citrate)	0.5 mg	55%
Potassium (as Potassium Nitrate)	190 mg	4%
Proprietary Blend Potassium Nitrate, Arugula Extract (*Eruca sativa*, leaf), Hesperidin (*Citrus sinesis, fruit peel*)	510 mg	**

*Percent Values are based on a 2,000 calorie diet
*Daily Value (DV) not established

Other ingredients: Rice Hull and Vegetable capsule contains water and hypromellose. Manufactured in a facility that processes Milk, Soy, Eggs, Peanut, Sesame, Shellfish, Tree Nuts and Wheat.



Oxalate crystals

Crystalline spiky, incredibly sharp molecules
Many people with chronic issues - hard time clearing oxalates
Especially with a B6 deficiency
Build up in kidneys, blood vessels, bones, joints, eyes, heart
Can cause a lot of pain
Increase kidney stone formation
Inhibit absorption of other nutrients, mainly minerals like calcium & magnesium
With increased fat in gut, calcium binds with fat not oxalate

High oxalate foods

Spinach
Beets
Soy
Almonds
Potatoes
Nuts
Chocolate

Summary

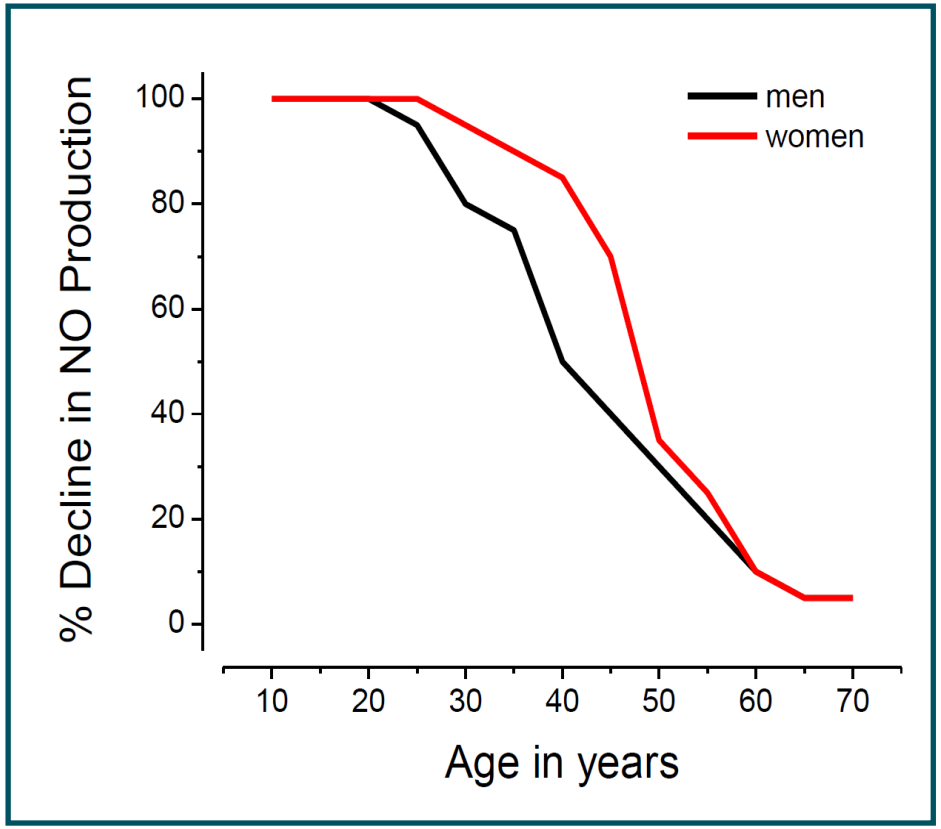
NO production naturally declines with age ~50% by the time we are 40
~15% by age 60

Optimization is possible

300-400mg nitrate necessary for physiological changes
Est US population ~150mg nitrate/day

Nitrate deficient population

Supporting the nitrate/nitrite/NO pathway not only increases NO directly, helps recouple NOS to increase NO through NOS pathway decreasing superoxide production, decreasing oxidative stress and increasing healthy longevity….



Thank You

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(310) 505-3896
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