EMF & Depletion of Nitric Oxide

Beth Shirley, RPh, CCN

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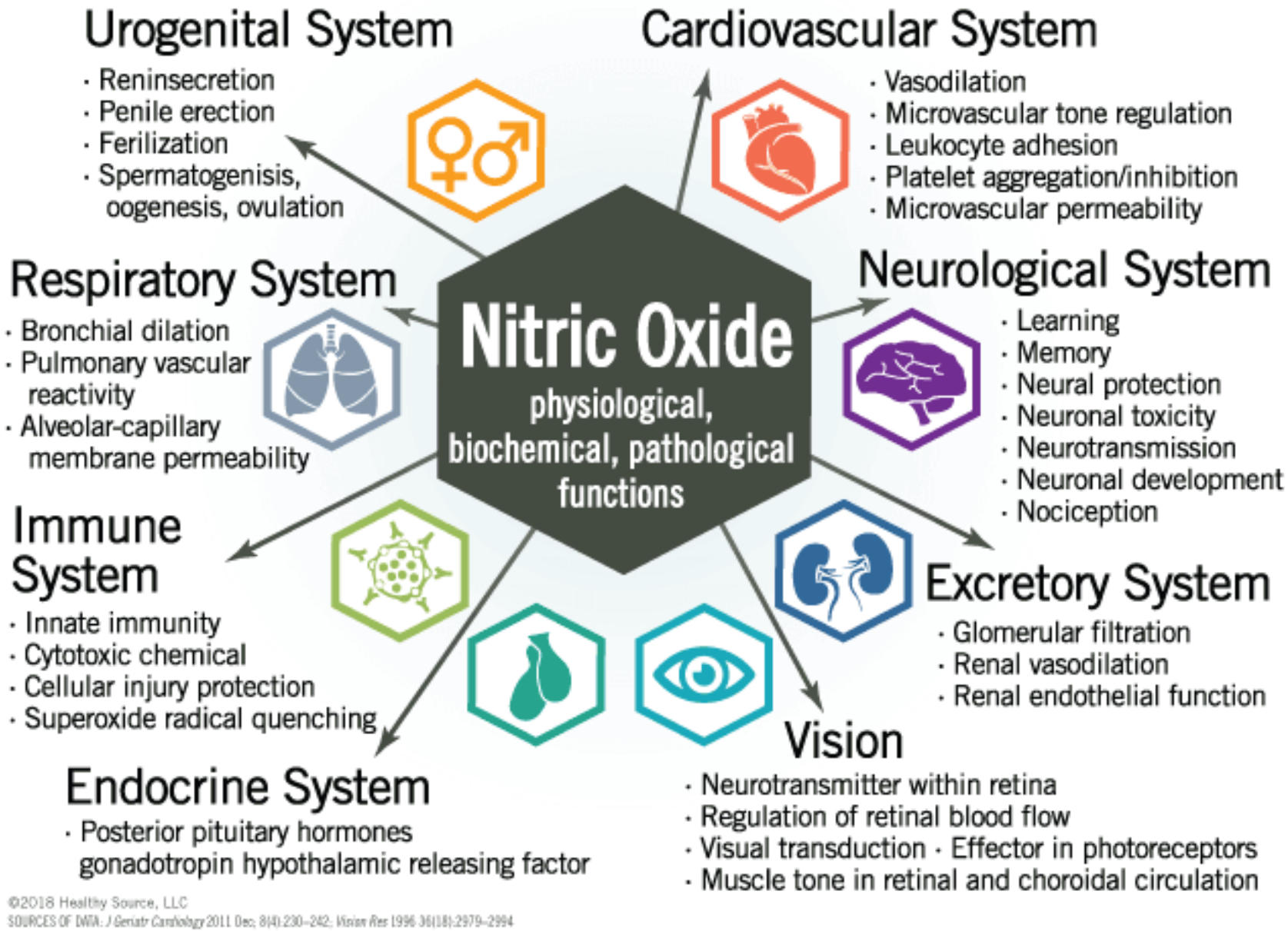
Beth developed an expertise as a pharmacist and certified clinical nutritionist during a 40+ year career. Her specialties include stress-induced hormonal imbalance, intestinal dysfunction, autoimmune and chronic inflammatory issues, detoxification, nutrigenomics and super-normal oxidative stress.

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 pleasure.

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

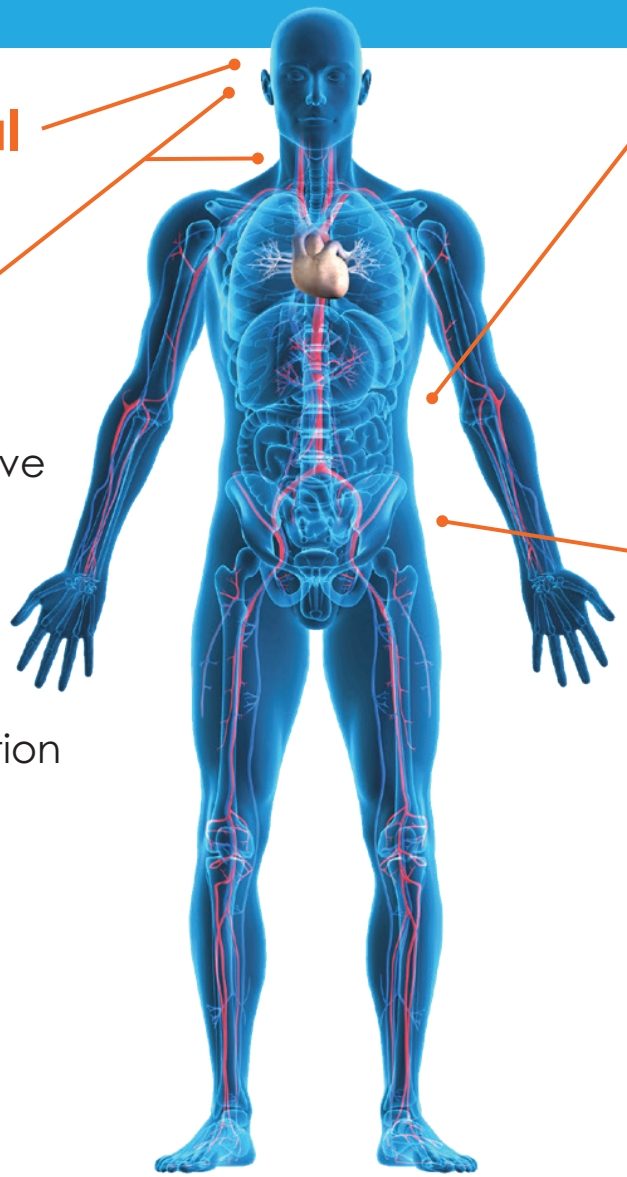
EMF Effects

Behavioral Psychological

- Anxiety/Depression
- ADD/OCD
- Stress/Emotional

Neurologic Effects

- Alzheimer's/Neurodegenerative diseases
- Cognitive dysfunction
- Learning/Memory
- Hypothalmic-Pituitary-Hormonal dysfunction
- Pineal/Thymus gland dysfunction
- Sleep disorders/Insomnia
- Brain tumors
- Tinnitus/Eye problems
- BBB disruption
- Microglial Inflammation
- Headaches



Immunological Effects

- Inflammation/Aging (Inflammaging)
- Imbalance (Th1/Treg–Th2/Th17 shift)
- Mast cell activation
- Stimulates pathogens
- Synergistic with toxins
- Autoimmunity

Cellular Effects

- Metabolic dysfunction/ Insulin resistance
- Mitochondrial dysfunction
- Cardiovascular dysfunction/HTN
- Fatigue/Weakness/Pain
- Cancers
- DNA damage/Epigenetic changes
- "Leaky gut"
- Infertility
- EMF sensitivity syndrome

EMR - waves of electric & magnetic energy moving through space together

EMF – spans large frequencies

Change in electrical charge changes biological processes

Quantum Decoherence & Loss of Energy Efficiency

Non-thermal RF effects mediates generation of ROS

Redox balance – oxidizing & reducing molecules relatively balanced

Oxidative stress – antioxidant defense insufficient or overwhelmed

- Disrupts structure and function of cells
- Change electric current in tissues
- Down-regulates production of NO

Role in All chronic, degenerative and inflammatory issues

Safety standards for nEMF exposure was last updated in 1996

Effects of electromagnetic fields exposure on the antioxidant defense system Doi:10.1016/j.jmau.2017.07.003

Non-thermal RF effects mediates generation of ROS

FIGURE 6.—Man being bombarded by "invisible" rays.

Why is NO so Essential?

- Regulates all CV function/homeostasis – circulation & microcirculation
- Hgb requires NO to be attached 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

Nitric oxide

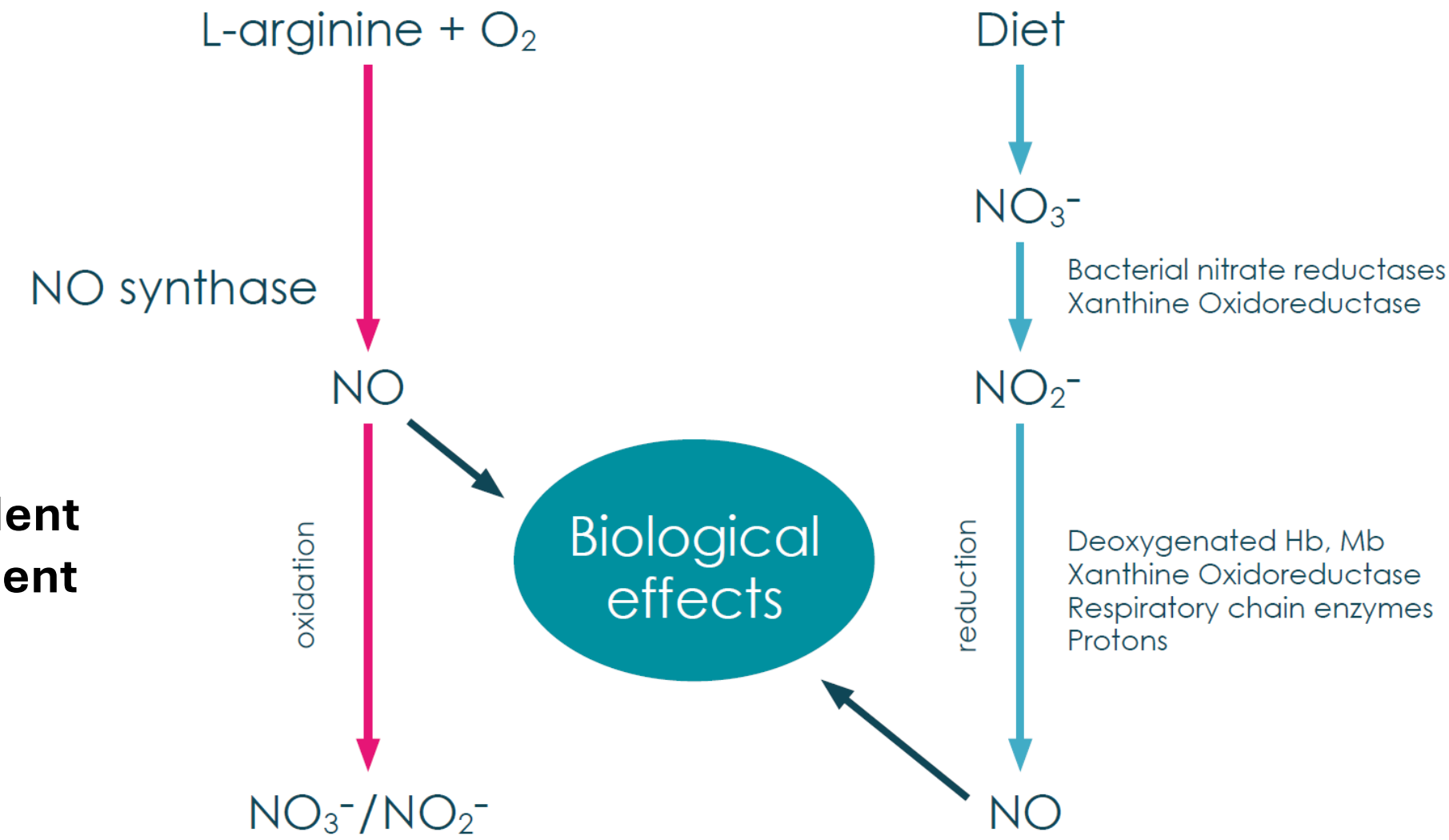
Why is NO so Essential?

- 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 telomorase activity

Nitric oxide

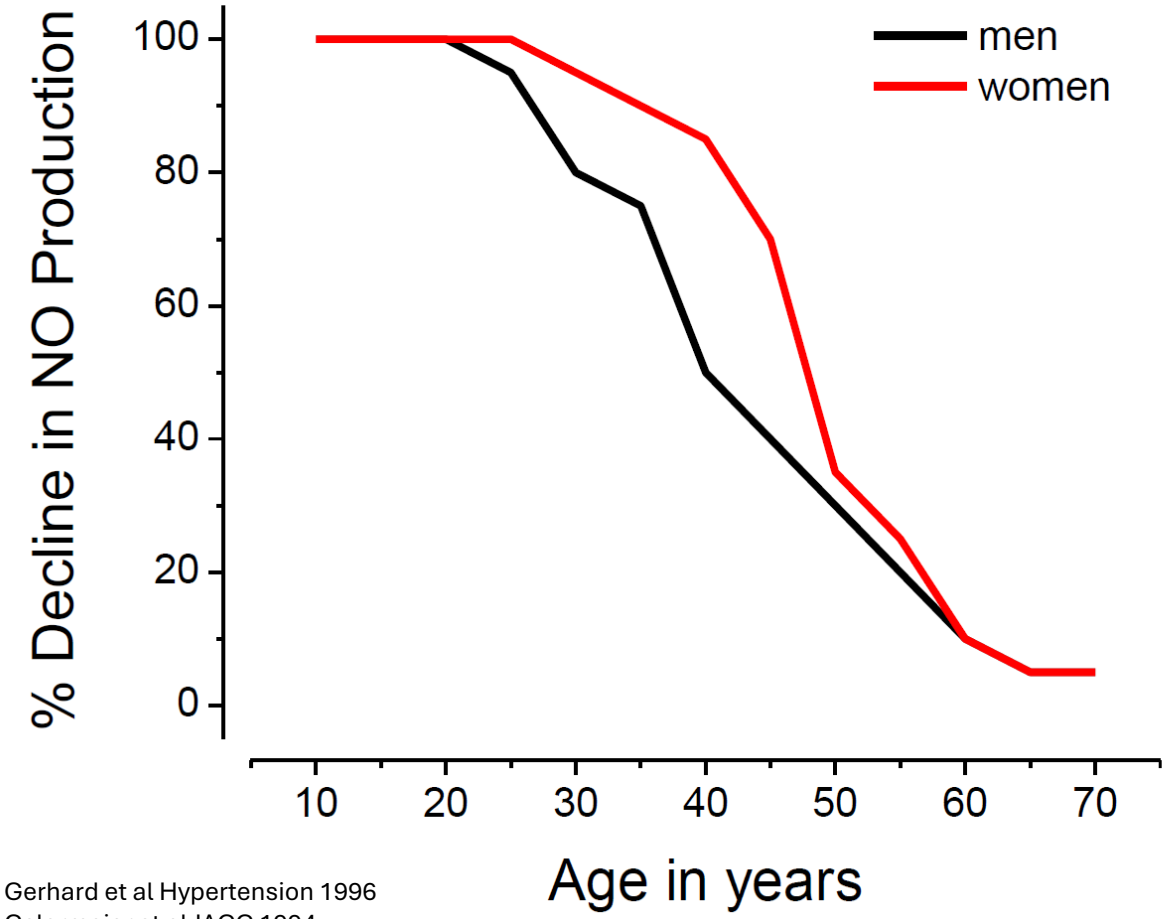
Arginine/NOS Pathway

Nitrate/Nitrite/NO Pathway



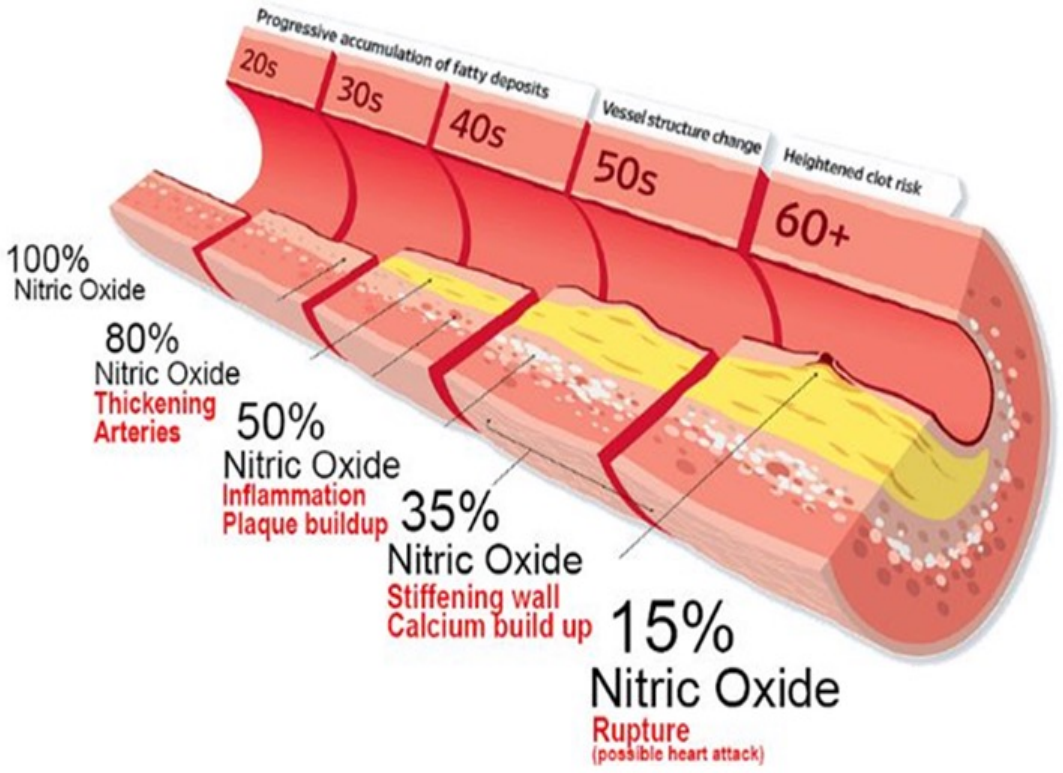
pH dependent
O2 dependent
FAD
FMN
NADPH
BH4
Fe

NO Production Decreases with Age



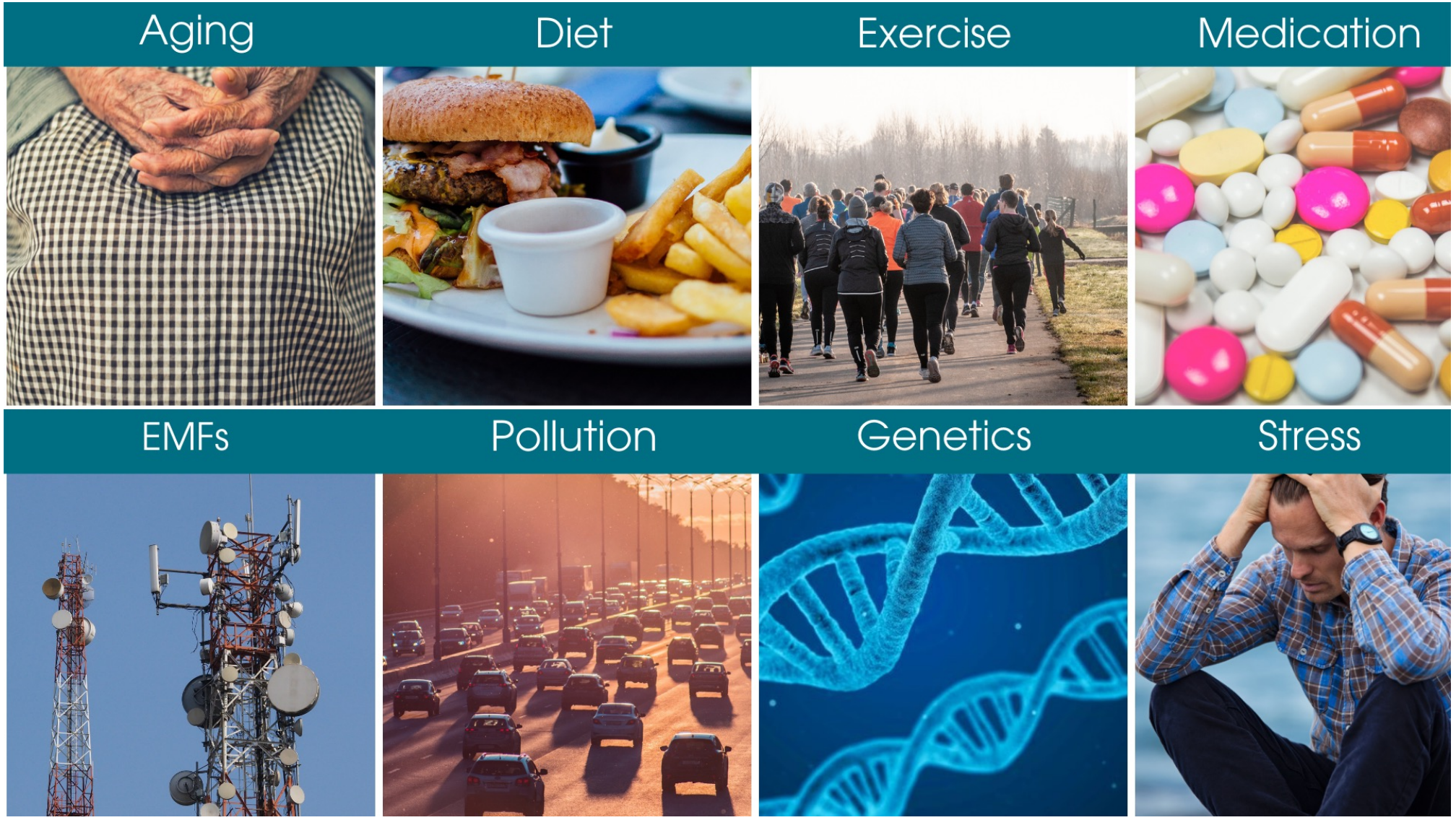
Gerhard et al Hypertension 1996
Celermajer et al JACC 1994
Taddei et al Hypertension 2001
Egashira et al Circulation 1993

Progression of Endothelial Dysfunction

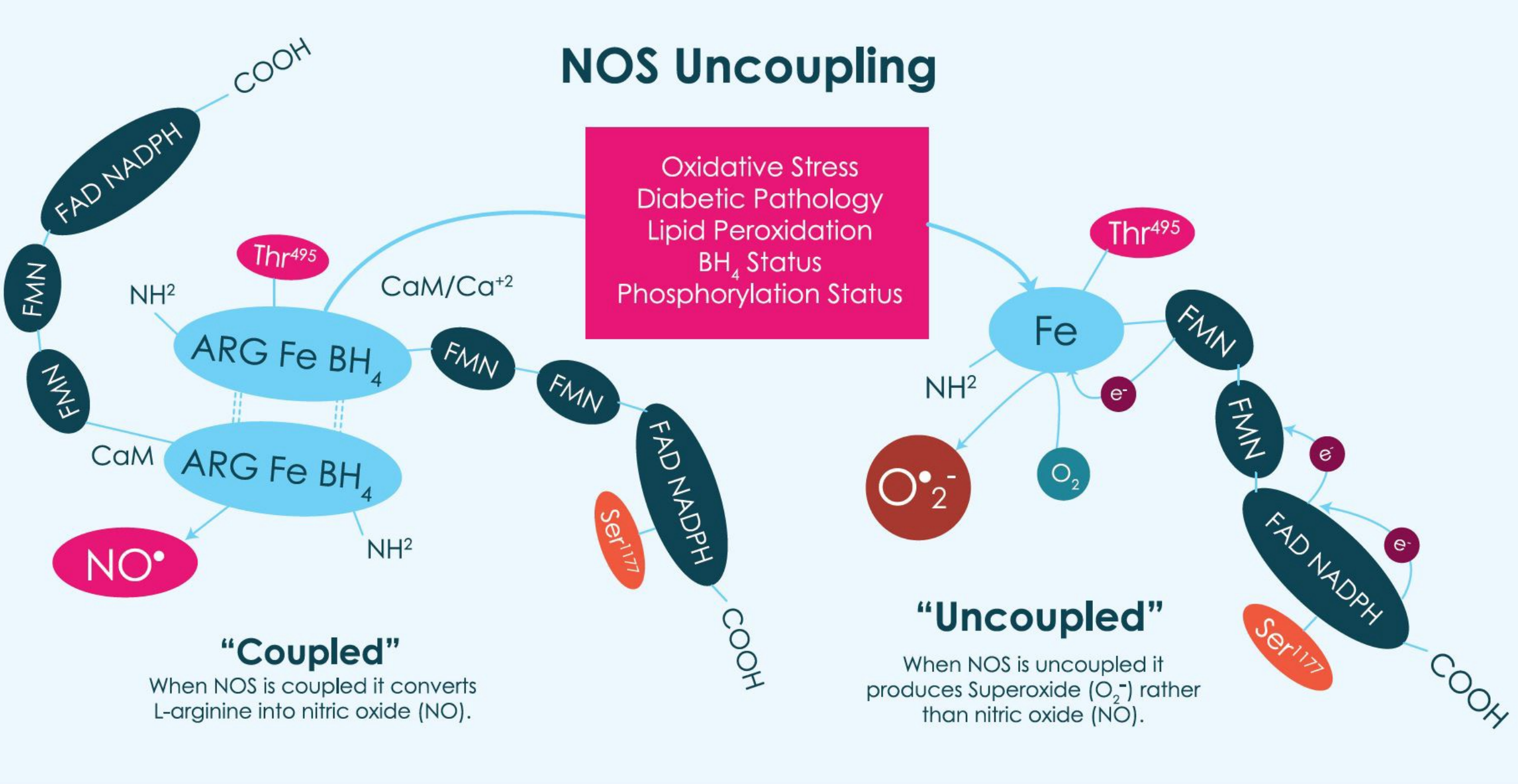


Bryan NS Curr Atheroscler Rep. 2018 Mar 17;20(5):21

Factors Affecting NO Production



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 - Not effective in aging population or anyone with any chronic 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

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 & NO inhibit NADPH oxidase
3) **Uncoupled mitochondrial ETC** – nitrite & NO recouple ETC

Oxidative stress & Inflammation – Base 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.

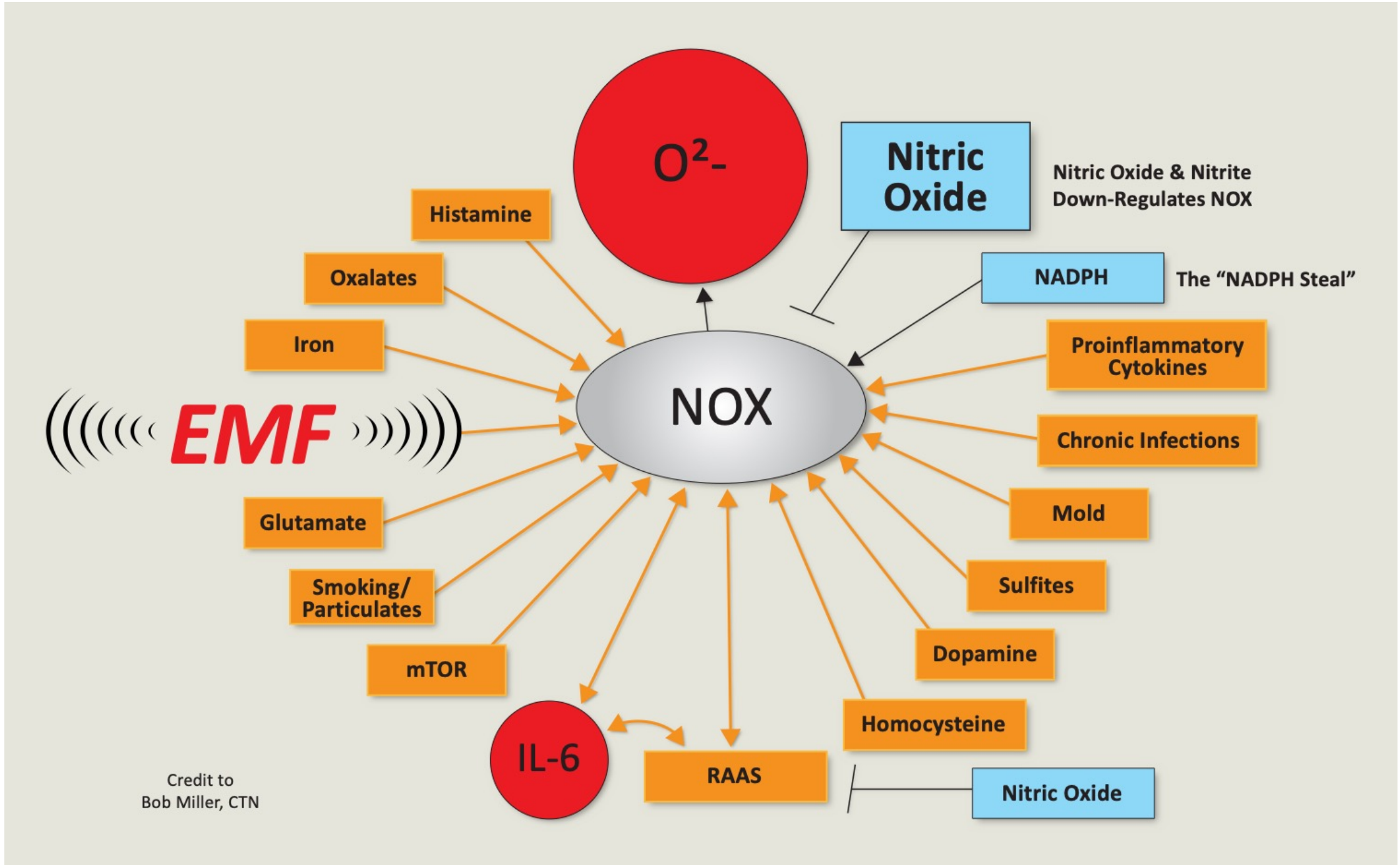
Bryan, NS. (Winter 2019). Are you Nitric Oxide deficient?. Retrieved from https://www.allergyresearchgroup.blog/are-you-nitric-oxide-deficient-part-2-of-2/ on April 17th 2023

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.

Nitrate positively affects NOS

Inhibits NADPH oxidase (NOX) decreasing superoxide & oxidative stress
Increases NADPH needed for other processes (NOS, recycling of GSH, steroid synthesis, fatty acid synthesis)
Nitrate up-regulates GTP cyclohydrolase-1 increasing BH4 production from GTP
BH4 recouples NOS increasing NO & decreasing superoxide
Increases activity of SOD & CAT
Scavenges free radicals decreasing oxidative stress

Nitrate increases NO through nitrate/nitrite/NO pathway, recouples NOS, reduces ROS and oxidative stress


O^{2-}
Nitric Oxide
Nitric Oxide & Nitrite
Down-Regulates NOX
Histamine
Oxalates
Iron
EMF
Glutamate
Smoking/
Particulates
mTOR
NOX
NADPH
The "NADPH Steal"
Proinflammatory
Cytokines
Chronic Infections
Mold
Sulfites
Dopamine
Homocysteine
Nitric Oxide
IL-6
RAAS
Credit to
Bob Miller, CTN

Initial stage of ROS production by EMF controlled by NADPH oxidase

Increases superoxide & oxidative stress

Activated by mTOR, histamines, oxalates, aluminum, iron, glutamate, smoking, homocysteine, sulfites, LPS, dopamine, RAAS, proinflammatory cytokines, EMF

'NADPH steal' resulting in decreased NADPH

- Impaired fatty acid synthesis
- Impaired steroid synthesis
- Decreased Phase 1 detoxification – cytochrome P450
- Decreased ability to recycle critical antioxidants, oxidized GSSG back to GSH
- Decreased ability to make NO

Nitrite and NO down-regulate NOX

Effects of electromagnetic fields exposure on the antioxidant defense system Doi:10.1016/j.jmau.2017.07.003

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

Supporting Nitrate/Nitrite/NO pathway down-regulates NAPDH oxidase

Peroxynitrite Theory of Damage from RF-EMF

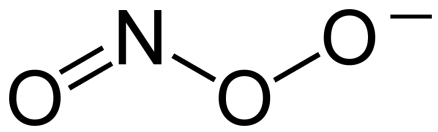
Martin Pall – pathophysiological response to EMFs result of stimulation of NO-cGMP protein kinase pathway
NO reacts with superoxide & forms peroxynitrite

Influx of Ca2+ increases Ca2+/calmodulin dependent increase in NO
Increased NO reacts with superoxide to increase ONOO-
Suggests ONOO- mechanism injuring cells & tissues
Data severely limited

NO may be present, however, this doesn't mean that NO is causing pathology

Electromagnetic fields act via activation of voltage gated calcium channels to produce beneficial or adverse effects doi:10.1111/jcmm.12088
) Activation of mitochondrial ATP-dependent potassium channels by nitric oxide doi.org/10.1161/01.CIR.101.4.439

Can Peroxynitrite be Measured?



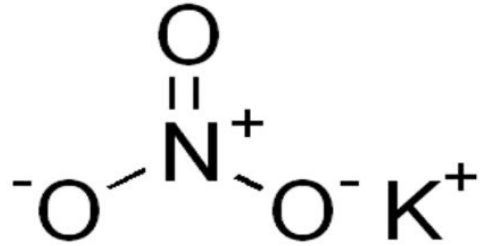
Measuring nitrotyrosine – **assuming** ONOO- was formed

Other nitrosating species can form nitrotyrosine (N2O3, N2O4, NO2 radical)

Not specific for ONOO-

New paradigm – ONOO- isomerizes to NO3- which is nitrate & inert

ONOO- in equilibrium with ONOOH (peroxynitrous acid) under physiologically relevant pH



ONOOH is unstable in aqueous solution & isomerizes to NO3-

ONOO- reacts with oxyHb – isomerizes to NO3- (90-95%)

Peroxiredoxins – significant biological sink of ONOO-

2 electron reduction of ONOO- to NO3-

Inhibit formation of ONOO- by inhibiting formation of superoxide

Peroxynitrite Decomposition Catalysts: Therapeutics for Peroxynitrite Mediated Pathology doi:10.1073/pnas.95.5.2659

Oxygen Radicals, NO & Peroxynitrite: Redoc Pathways in Molecular Medicine doi.org/10.1073/pnas.1804932.115

ONOO- is formed when NO is in close proximity to Superoxide
In general – if making lots of superoxide, typically not making lots of NO
Superoxide shuts down NO production

Controversial - increased NO from iNOS or any other source injures cells
L-NAME (NOS inhibitor) – see decrease in tissue injury & inflammation
May not be due to inhibition of cytotoxic concentrations of NO production
Other actions of L-NAME may be at play here
Large amounts of NO does Not cause damage to mucosa or vasculature

Restoring NO production decreases O2-, thus decreasing ONOO- production decreasing ROS, RNS and oxidative stress

Oxygen Radicals, NO, and ONOO-: Redox Pathways in Molecular Medicine doi.org/10.1073/pnas.1804932115
Role of NO as a Mediator of GI Mucosal Injury? Say It Ain't So doi:10.1155/S0962935195000640

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.

EMF - extensive electron leakage from ETC

- Uncouples mitochondrial ETC
- Oxidative damage to membrane
- Down-regulation of antioxidant genes – SOD, CAT, GPx
- Changes macronutrients metabolism - lose ability for beta oxidation

Blue light exposure & EMF = hypoxia

Oxygen – essential cofactor in NOS enzyme

Nitrite: a physiological store of nitric oxide and modulator of mitochondrial function doi.org/10.1016/j.redox.2012.11.005
New evidence for cross talk between melatonin and mitochondrial mediated by a circadian-compatible interaction with NO doi.org/10.339o/ijms140611259

EMF Increases Superoxide & Oxidative Stress

Activates NADPH oxidase (NOX)

Uncouples mitochondrial ETC

Uncouples NOS

Increases activity of MPO increasing H2O2

Stimulates Fenton Reaction – OH- & Fe3+

Increases intracellular influx of Ca2+ simulating NADPH oxidase

Increases activity, concentration & lifetime of ROS

CACNA1C – gene that encodes VGCC and increased intracellular calcium

- Excitotoxicity & oxidative stress
- Increased sensitivity to EMF
- Gene associated with bipolar, schizophrenia & increased intracellular Ca2+

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

Investigation of the effects of distance from sources on apoptosis, oxidative stress and cytosolic calcium accumulation via TRPV1 channels induced by mobile phones and Wi-Fi in breast cancer cells doi.org/10.1016/j.bbamem.2015.02/013

Stimulation of Ca2+ Channels by EMF

VGCC – gated ion channel in membrane of excitable cells

- Widely distributed within CNS
- Loss of membrane potential causing proton leak from mitochondria
- Decreased energy for ATP synthesis
- Increasing ROS within mitochondria – mitochondrial uncoupling
- Cytotoxicity – weaken neuronal integrity
  - Breakdown of cytoskeleton
  - Dilatation of endoplasmic reticulum
  - Cytosolic shrinkage – dehydration of cell
- Activation of NMDA – component of inflammatory & neuropathic pain
  - GABA inhibits subunit of VGCC
- **Pathophysiology of CNS disorders including ALZ, PD and MS**

Electromagnetic fields act via activation of voltage gated calcium channels to produce beneficial or adverse effects doi:10.1111/jcmm.12088
Role of calcium permeable channels in pain processing doi:10.5772/intechopen.77996
Mitochondrial uncoupling, ROS generation and cardioprotection doi:org/10.1016/j.bbabio.2018.05.019

NO Modulates Ca2+ influx

NO donors inhibits Ca2+ current in voltage-independent manner

Direct action on channel protein by S-nitrosylation
Indirect action – activation of cGMP increasing intracellular levels
    NO's ability to activate Na+ channels in baroreceptors & hippocampal neurons

NO inhibition of Ca2+ current
    Regulates intracellular Ca2+ concentration
    Synaptic transmission

NO - an endogenous mitochondrial K/ATP channel opener, recouples mitochondria optimally blunting mitochondrial Ca2+ overload without undermining ATP synthesis

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

Exposure to w-fi increases heart rate & bp

increases arrhythmias

Enhances hypertension & dyslipidemia

Stimulates RAAS increasing aldosterone

NO governs circulation and microcirculation

Down-regulates RAAS

NO/cGMP pathways activates large Ca2+ dependent K+ channels which leads to membrane hyperpolarization & closure of VGCC inhibiting Ca2+ influx

NO regulates All mechanisms controlling intracellular Ca2+

Effects of acute exposure to Wi-Fi signals (2.45 GHz) on heart rate variability and blood pressure in albino rabbits doi.org/10.1016/j.etap.2015.08.015
Foundation for Mind-Being Research fmbr.org editorial Jan 2016
Nitric oxide signaling in CNS Annual review of Physiology doi:10.1146/annurev.ph.57.030195.003343
Nitric oxide and voltage-gated Ca2+ channels doi:10.1007/978-1-59259-806-9_7

EMF, Impaired Immune Response & Impaired NO Production

EMF classified as immunosuppressant

Causes biological stress response

Down-regulates production of NO

NO – essential for defense against pathogens

Alters gut-brain-immune axis

Increased Ca2+ influx – significantly increased cytokine storms

Increased cytokine storms - increased susceptibility

Long term stress (EMF exposure) dysregulates immune response

80% of immune system in gut

Intensifies reactions to mold, lyme, virus, bacteria, parasites

Oxidative stress down-regulates NO production

Major Beneficial Actions of NO on GI Tract

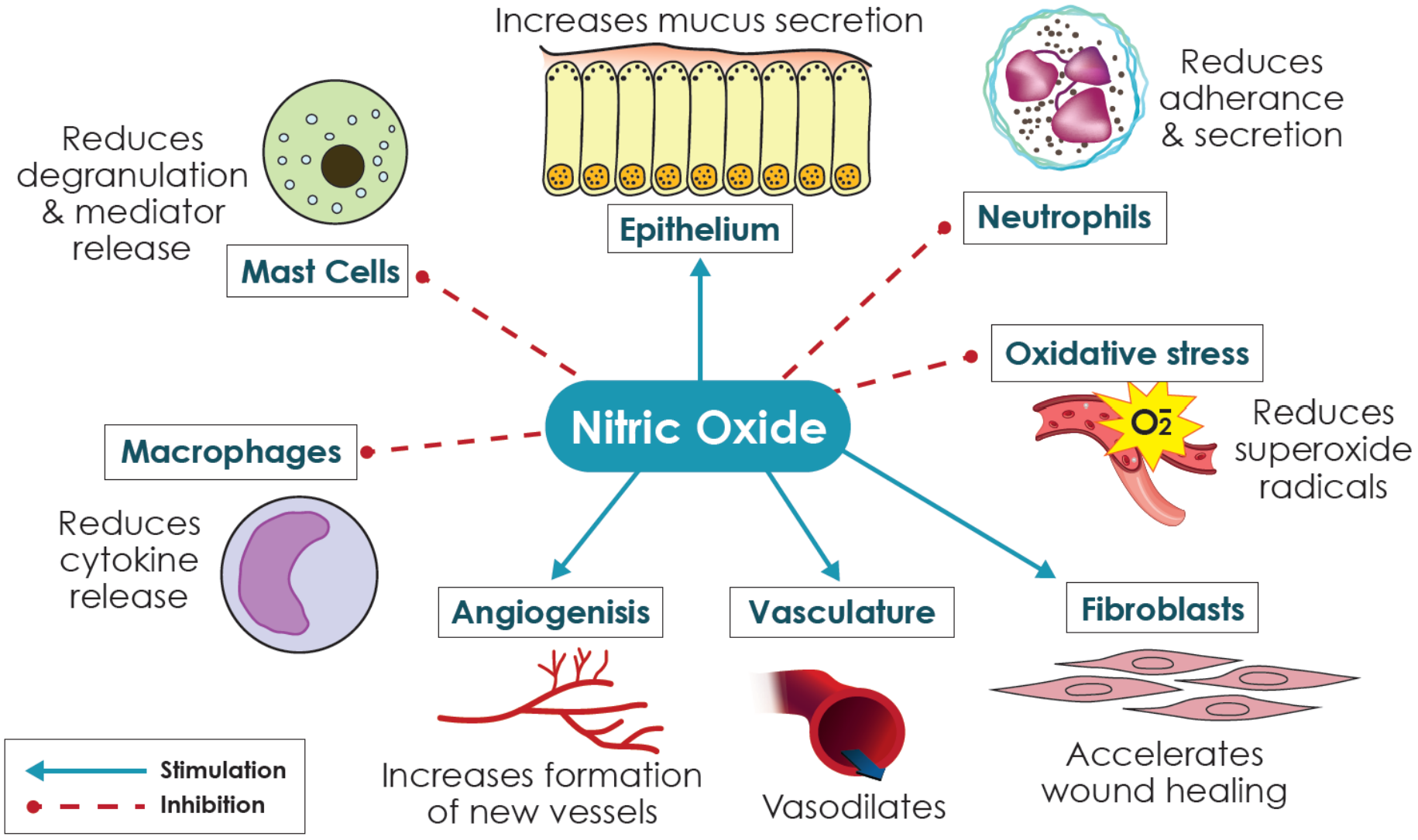


Diagram: Magierowski, M.; Magierowska, K.; Kwiecien, S.; Brzozowski, T. Gaseous Mediators Nitric Oxide and Hydrogen Sulfide in the Mechanism of Gastrointestinal Integrity, Protection and Ulcer Healing. *Molecules* 2015, 20, 9099-9123.

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 - breakdown of the barrier - leaky gut, leaky brain

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

EMF Stimulates Mast Cell Degranulation

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 & cytokines
- Inhibit leukocyte endothelial cell attachment
- Inhibit generation of ROS by mast cells

EMF/Microbiome Disruption

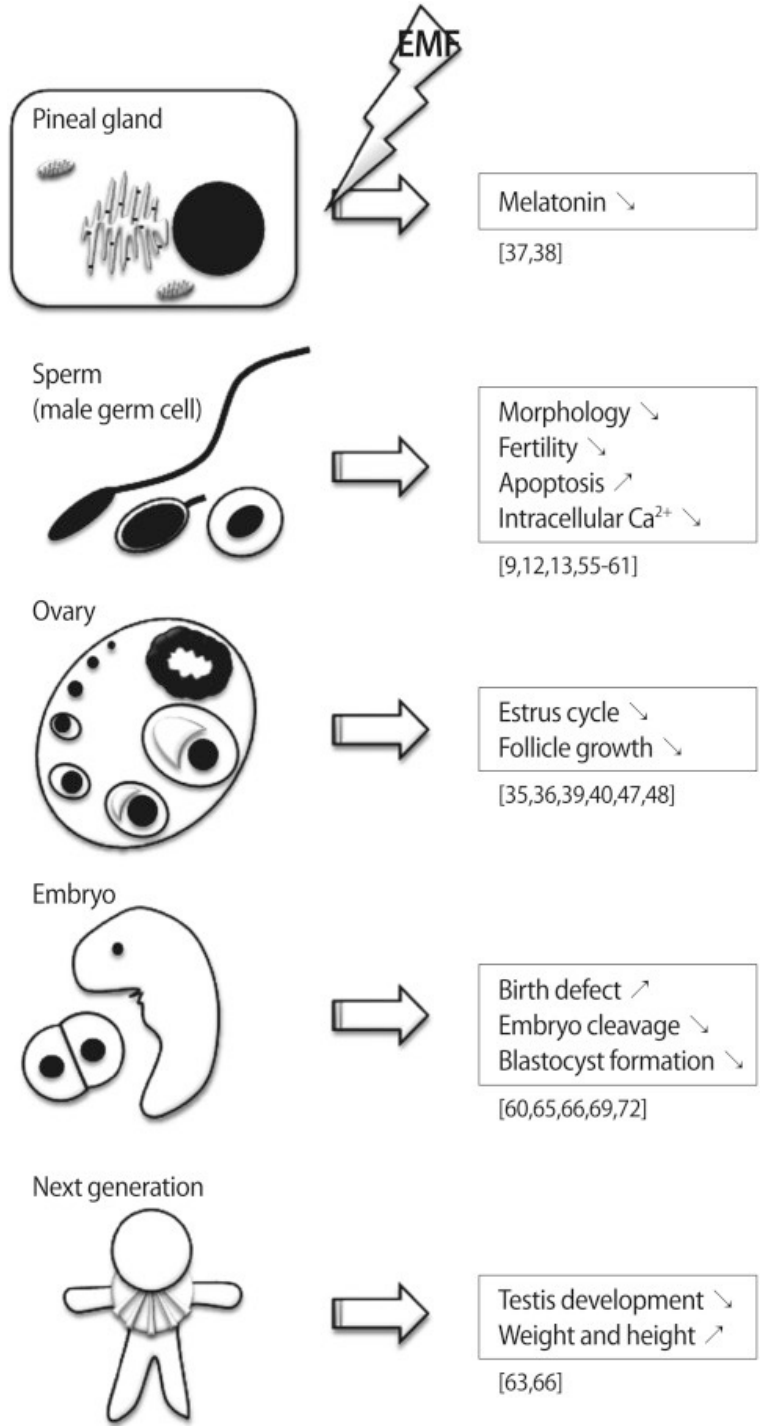
Environmental pollutant capable of disrupting microbiomes
Increasing antibiotic resistance
Enhancing biofilm formation
Decreasing good bacteria while increasing harmful
Beneficial bacteria grow slower

Supporting nitrate/nitrite/NO pathway

- Prevent dysbiosis
- Supports healthy microbiomes
- Decrease inflammatory pathways
- Down-regulates and scavenges ROS
- Nitrite disrupts protective biofilms

The response of human bacteria to static magnetic field and RF-EMF DOI:10.1007/s12275-017-7208-7
Evaluation of wi-fi radiation effects on antibiotic susceptibility, metabolic activity and biofilm formation by E Coli 015747, S aureus and S epidermis DOI: 10.31661/jbpe.v0i0.1106

EMF exposure
Alters cellular homeostasis
Endocrine function
Reproductive function
Fetal development



Effects of EMF exposure on the reproductive system
doi.org/10.5653/cerm.2012.39.1.1

EMF, Infertility & NO -
Powerful Promoter of Infertility

EMF – high penetration ability:
Destructive, non-thermal effects

Disrupts brain functions:
Dysregulates HPA axis –
Fight/Flight/Freeze
Biological stress response increasing cortisol
Upregulation of sympathetics
Downregulation of parasympathetics

Neuroendocrine changes:
Disrupt hypothalamus
Decrease GnRH
Decrease LH & FSH release

Inhibit melatonin release:
Increase oxidative stress
Influences LH & FSH release

Stress and the female reproductive system. Doi:10.1016/j. jri.2003.09.004
A review on electromagnetic fields (EMFs) and the reproductive system. Doi.org/10.19082/2655
Reducing oxidative/nitrosative stress: a newly discovered genre for melatonin. Doi. org/10.1080/10409230903044914
Long term exposure of 2450MHz electromagnetic radiation induces stress and anxiety like behavior in rats. Doi:10.1016/jneuint.2019.04.001
Adverse health effects of 5G mobile networking technology under real-life conditions. Doi.org/10.1016/ jtoxlet.2020.01.020

EMF & Infertility

Most EMF studies on animals

Some cases of spontaneous abortions & fetal abnormalities in pregnant women

Inhibits ovulation
Decrease # of corpora lutea
Accelerated apoptosis in ovaries
Deleterious to implantation
Negative effects in early development of embryo

Decrease sperm count, morphology, motility & viability
Disrupt sperm mitochondria

A review on electromagnetic fields (EMFs) and the reproductive system. Doi.org/10.19082/2655
Radiation and male fertility. Doi.org/10.1186/s12958- 018–0431–1

EMF & Infertility

Stimulates NADPH oxidase increasing superoxide & oxidative stress

Extensive electron leakage from ETC

Disrupts normal cellular process of sperm, oocytes and embryos

Increase Ca2+ influx through VGCC increasing oxidative stress

Uncouples NOS

Increase activity, concentration & lifetime of ROS

Increase GI & BBB permeability

Disrupts microbiome

Increase leaky gut and leaky brain

Health of gut intimately connected to infertility

A review on electromagnetic fields (EMFs) and the reproductive system. Doi.org/10.19082/2655
Radiation and male fertility. Doi.org/10.1186/s12958- 018–0431–1
Radiation from wireless technology affects the blood, the heart, and the autonomic nervous system. Doi:10.1515/ reveh-2013–0004

EMF increases HbA1C and T2D

Environmental – Type 3 Diabetes

Increased plasma glucose & blood viscosity

Long term exposure to activated mobile phones

Increases fasting blood glucose &insulin

EMF – physiological stress response (increase cortisol which increase glucose)

Blood sugar dysregulation – uncouples NOS

HbA1c binds NO tightly

Supporting nitrate/nitrite/NO pathway optimizes NO

Downregulates oxidative stress & pro-inflammatory cytokines

Downregulates RAAS

Essential for GLUT 4 translocation

Association of exposure to radio-frequency electromagnetic field radiation (RF-EMFR) generated by mobile phone base stations with glycated hemoglobin (HbA1c) and type 2 diabetes mellitus Journal of Diabetes and Metabolism 7th Indo Global Diabetes Summit and Medicate Expo Nov 23-25, 2015 Bengaluru, India

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

EMF Can Stimulate iNOS

Chronic inflammatory processes

Infections –bacterial, viral, fungal, parasitic

Environmental factors – EMF, Al, Hg, U, Fe, BPA, HFCS, gluten, chlorine, glyphosate, homocysteine

iNOS can produce up to 1000X greater NO than eNOS

- **NOS must be coupled to produce NO**
- **Uncoupled NOS produced superoxide**

Upregulated iNOS downregulates eNOS & nNOS

Impaired eNOS & nNOS

- Decreased delivery of glucose, oxygen & nutrients
- Decreased clearing away of cellular debris

Harmful to essential vital organs – brain, heart, kidneys, liver, lungs, etc.

EMF Impairs BBB

Altered BBB integrity after exposure to EMF

Leakage of albumin

Serious neuronal cell damage

Tight junction proteins

BBB, eyes, intestinal tract, skin, kidney, bile duct

Loss of tight junction proteins – breakdown of barrier

Decreased expression of occludin and claudin 5

Leaky gut means leaky brain

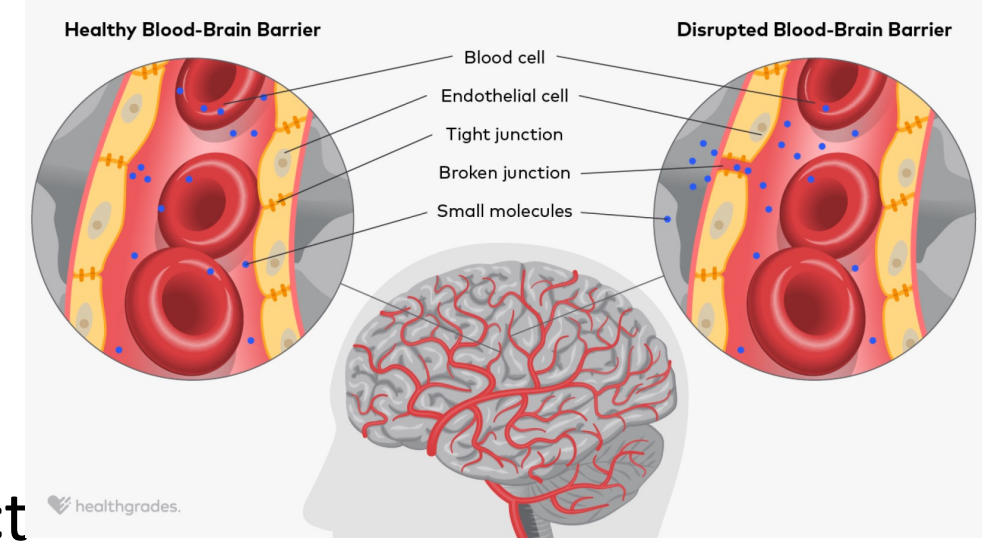
Nitrate increase rebound levels of occludin & claudin 5

protecting tight junction proteins & barrier integrity

BDNF – affects integrity of tight junctions

Homeostatic regulator of barrier integrity

NO – essential mediator of BDNF



Increased BBB permeability in mammalian brain 7 days after exposure to the radiation from a GSM-900 phone doi:10.1016/j.pathophys.2009.01.001
Nerve cell damage in mammalian brain after exposure to microwaves from GSM mobile phones doi:10.1289/ehp.6039

EMF Stimulates mTOR

mTOR – mechanistic target of rapamycin

Regulate cell growth, proliferation, motility, survival, protein synthesis, autophagy, activates insulin receptors & IGF1

Swimming in sea of mTOR stimulation

mTOR stimulates NADPH oxidase

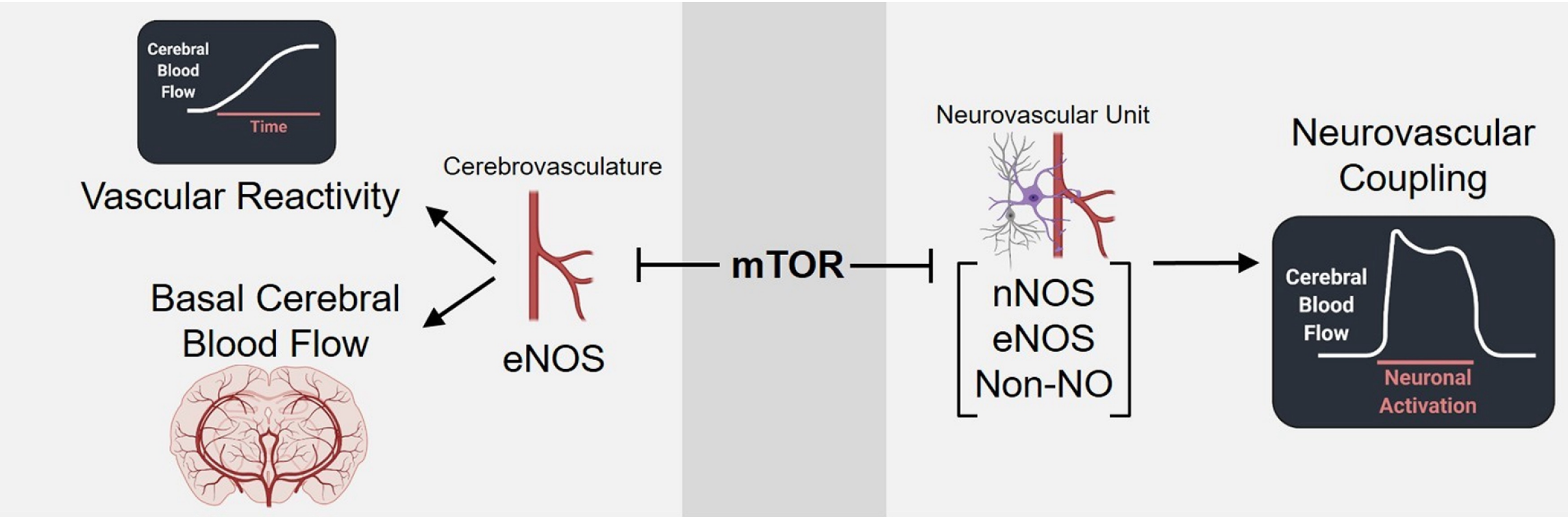
mTOR drives cerebrovascular dysfunction by down-regulating eNOS

mTOR inhibits AMPK & autophagy

AMPK – essential in glucose & lipid metabolism, mitochondrial metabolism (autophagy, mitophagy)

Virus co-opt mTOR – make host more hospitable for replication

mTOR attenuation with rapamycin reverses neurovascular uncoupling and memory deficits in mice modeling of Alzheimer's Disease doi:10.1523/JNEUROSCI.2144-20.2021
Activation of mTOR/p7056 kinase by Ang 11 inhibits insulin-stimulated endothelial NOS and vasodilation doi:10.1152/ajpendo.00497.2011



Activation of mTOR/p7056 kinase by Ang 11 inhibits insulin-stimulated endothelial NOS and vasodilation doi:10.1152/ajpendo.00497.2011

EMF Increases Cell Senescence

Decreased mTOR activity increases life span

- Increases autophagy – removal of dysfunctional cellular components
- Clearance of debris before stimulation of apoptosis
- Maintains cell viability and homeostasis

Senescence – cells stop dividing and lose their function

- Irreversible growth arrest
- Contributes to pathogenesis of atherosclerosis
- Increased ROS in cells from cell phones

NO & NO donors stimulates AMPK which blocks mTOR & allows autophagy

NO can prevent endothelial senescence

NO scavenges ROS

NO increases telomerase activity to restore telomere length

Continuous exposure to 1.7 GHz LTE electromagnetic fields increases intracellular ROS to decrease human cell proliferation and induce cell senescence doi:10.1038/s41598-020-65732-4
mTOR/Autophagy www. Nutrigeneticresearch.org
Endothelial cellular senescence is inhibited by NO: implications in atherosclerosis associated with menopause and diabetes doi:10.1073/pnas.06007873103
Adapting the stress response: viral subversion of the mTOR signaling pathway DOI:10.3390/v8060152

Telomerase & Telomere Shortening

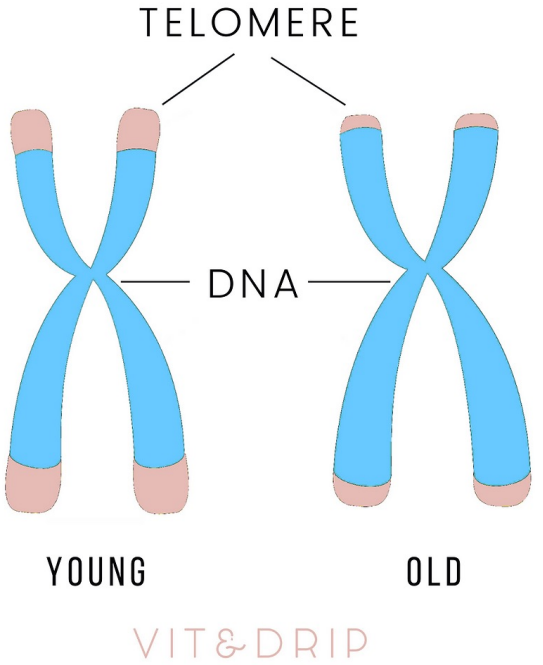
Chronic oxidative stress, due to long term exposure of environmental factors, like EMF
Increases telomere shortening

Nitric Oxide:

- Decreases ROS production
- Scavenges ROS
- Inhibits NADPH oxidase

Increased Nitric Oxide bioavailability:

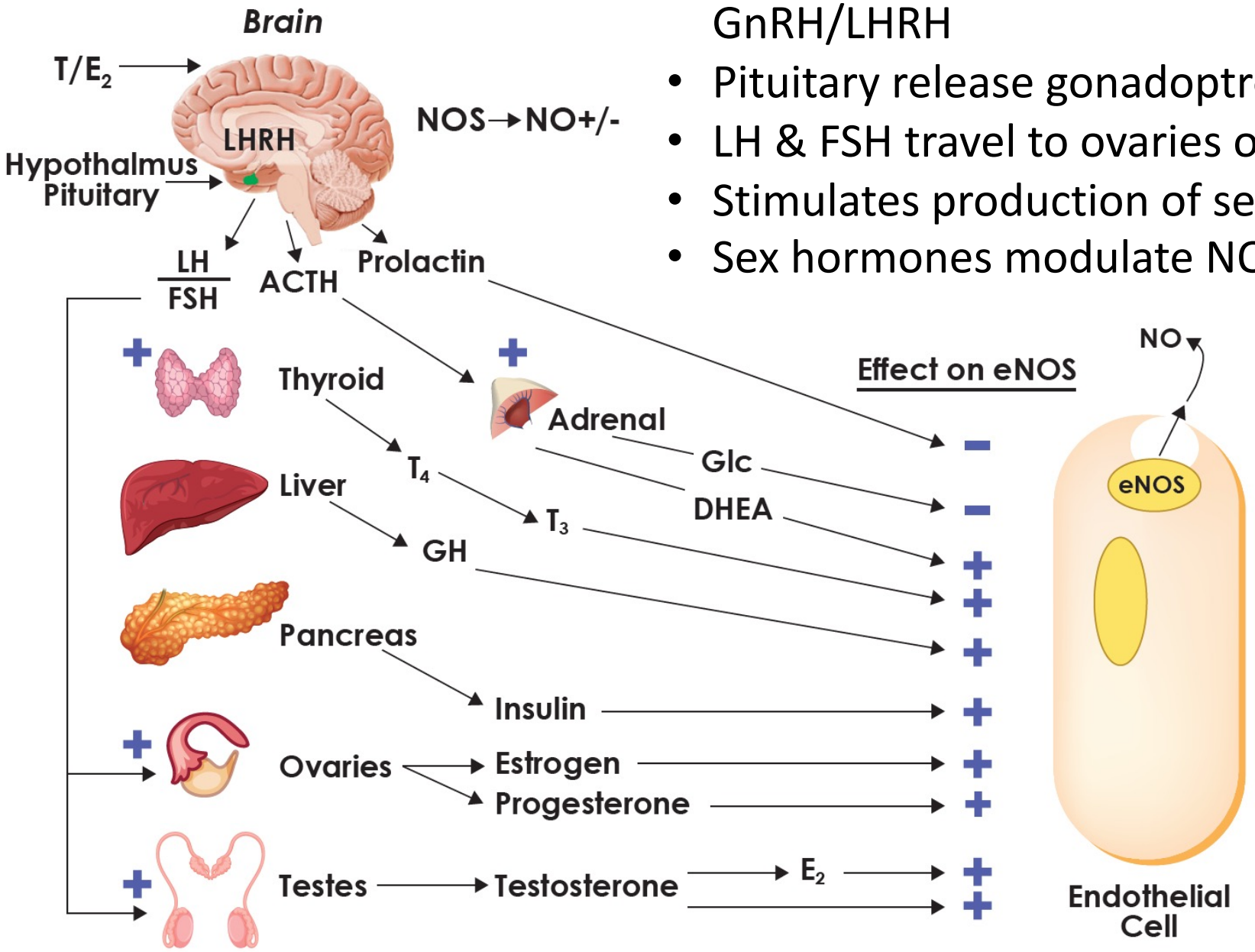
- **Activates telomerase**
- **Inhibits cellular aging**
- **Delays cellular senescence**



https://www.researchgate.net/publication/319534014_A_Review_of_the_Effects_of_Electromagnetic_Fields_on_Telomere-Dependent_Life_Span_in_Human_and_Experimental_Animal_Models
Stress and the female reproductive system. Doi:10.1016/j. jri.2003.09.004
Lifestyle and fertility: the influence of stress and quality of life on male fertility. Doi:10.1186/s12958–018–0436–9

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



EMF – Biological Stress Response

Dysregulation of HPA axis

Increased plasma glucocorticoid levels

Impair growth of neural cells in hippocampus – learning & memory

Increases Heat Shock Proteins – marker of cells under stress

Every cell in body is in alarm state from EMF/ER as per Dr Klinghardt

Cortisol down-regulates iNOS & eNOS

Increases ROS increasing oxidative stress

Decreases synthesis of BH4 – uncoupling NOS

Increases blood glucose

Increases HbA1C – tightly binds NO

All of these decrease production of/or make NO not bio-available

Investigation of the effects of distance from sources on apoptosis, oxidative stress and cytosolic calcium accumulation via TRPV1 channels induced by mobile phones and Wi-Fi in breast cancer cells doi.org/10.1016/j.bbamem.2015.02/013

Long term exposure of 2450 MHz electromagnetic radiation induces stress and anxiety-like behavior doi:org/10.1016/jneuint.2018.04/001

EMF & Thyroid

Decreased T3 and T4 in serum
Increased cortisol – decreases conversion of T4 to T3
Increased degranulation of mast cells in thyroid

NADPH oxidase (NOX) enzymes in thyroid - DUOX1 & DUOX2
Increase ROS, O2- and H2O2
Need precise amount of H2O2 for TPO

NO & nitrites inhibit NOX & DUOX enzymes
Supporting Nitrate/Nitrite/NO pathway may be an underutilized thyroid therapy due to its role in decreasing production of superoxide & other ROS by optimizing NO levels, scavenging ROS & supporting healthy circulation & microcirculation

Effects of 900 MHz electromagnetic field and TSH and thyroid hormones in rats doi.org/10.1016/j.toxlet.2005.03.006
Stereological analysis of thyroid mast cells in rats after exposure to extremely low frequency electromagnetic field and the following "off" field period
2005;56(1-2):43-51. doi: 10.1556/ABiol.56.2005.1-2.5.

EMF – sleep interference

- Phase shifting of circadian biology
- Disruption of brain activity during sleep
- Increased BBB permeability
- Increased cortisol
- Suppressed levels of melatonin

Most melatonin made within mitochondria (<5% in pineal) – gut health essential

Constant light exposure in pineal decreased NOS activity – 80% after 8 days

NO modulates circadian rhythm

Nitric oxide signaling in CNS Annual review of Physiology doi:10.1146/annurev.ph.57.030195.003343
Melatonin in the context of the reported bioeffects of environmental electromagnetic fields doi:10.1016/s0302-4598(98)00152-4
Effect of melatonin on cardiovascular risk factors and metabolic syndrome: a comprehensive review doi:10.1007/s00210-01822-4
New evidence for cross talk between melatonin and mitochondrial mediated by a circadian-compatible interaction with NO doi.org/10.339o/ijms140611259

Melatonin – potent free radical scavenger, especially OH-

Induces eNOS, nNOS

Inhibits iNOS

Stimulates GCL (glutamyl cysteine ligase) – rate limiting enzyme in GSH

Inhibits NADPH oxidase

Stimulates SOD

Decreases ADMA

Decreases proinflammatory mediators

Protective against mercury

Beneficial in non-dipper hypertension

Protective in OSA

NO chemistry modulates mitochondrial circadian cycle

Nitric oxide signaling in CNS Annual review of Physiology doi:10.1146/annurev.ph.57.030195.003343
Melatonin in the context of the reported bioeffects of environmental electromagnetic fields
doi:10.1016/s0302-4598(98)00152-4
Effect of melatonin on cardiovascular risk factors and metabolic syndrome: a comprehensive review doi:10.1007/s00210-01822-4
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EMF & Anxiety & Depression

VGCC – high density throughout nervous system

Activation - excitotoxicity

Microwave frequency produce widespread neuropsychiatric effects

- Depression
- Anxiety
- Irritability
- Sleep disturbance

Neurotransmitter imbalance

- Decreased serotonin, dopamine and PEA
- Increased norepi & epi – stress neurotransmitters

Microwave frequency electromagnetic fields (EMF) produce widespread neuropsychiatric effects including depression doi.org/10.1016/j.chemneu.2015.08.001
Changes of Clinically Important Neurotransmitters under the Influence of Modulated RF Fields—A Long-term Study under Real-life Conditions. *Electromagnetic Fields*. 2011;24(1):44-57

NO Involved in regulation of anxiety

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

Mediates neuroprotective actions of BDNF

Promotes neuronal survival

Stimulates neurogenesis

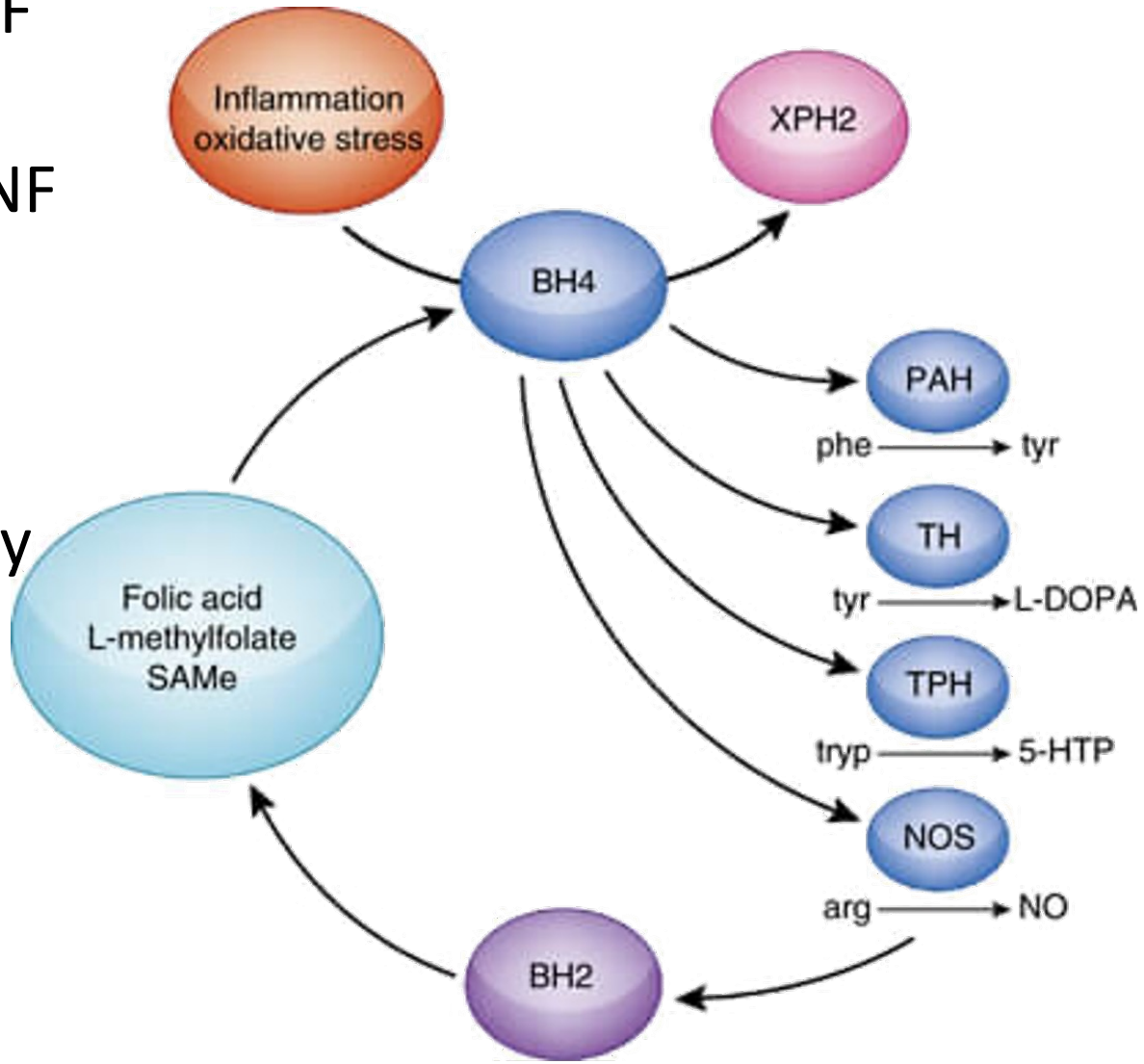
Enhances learning & memory

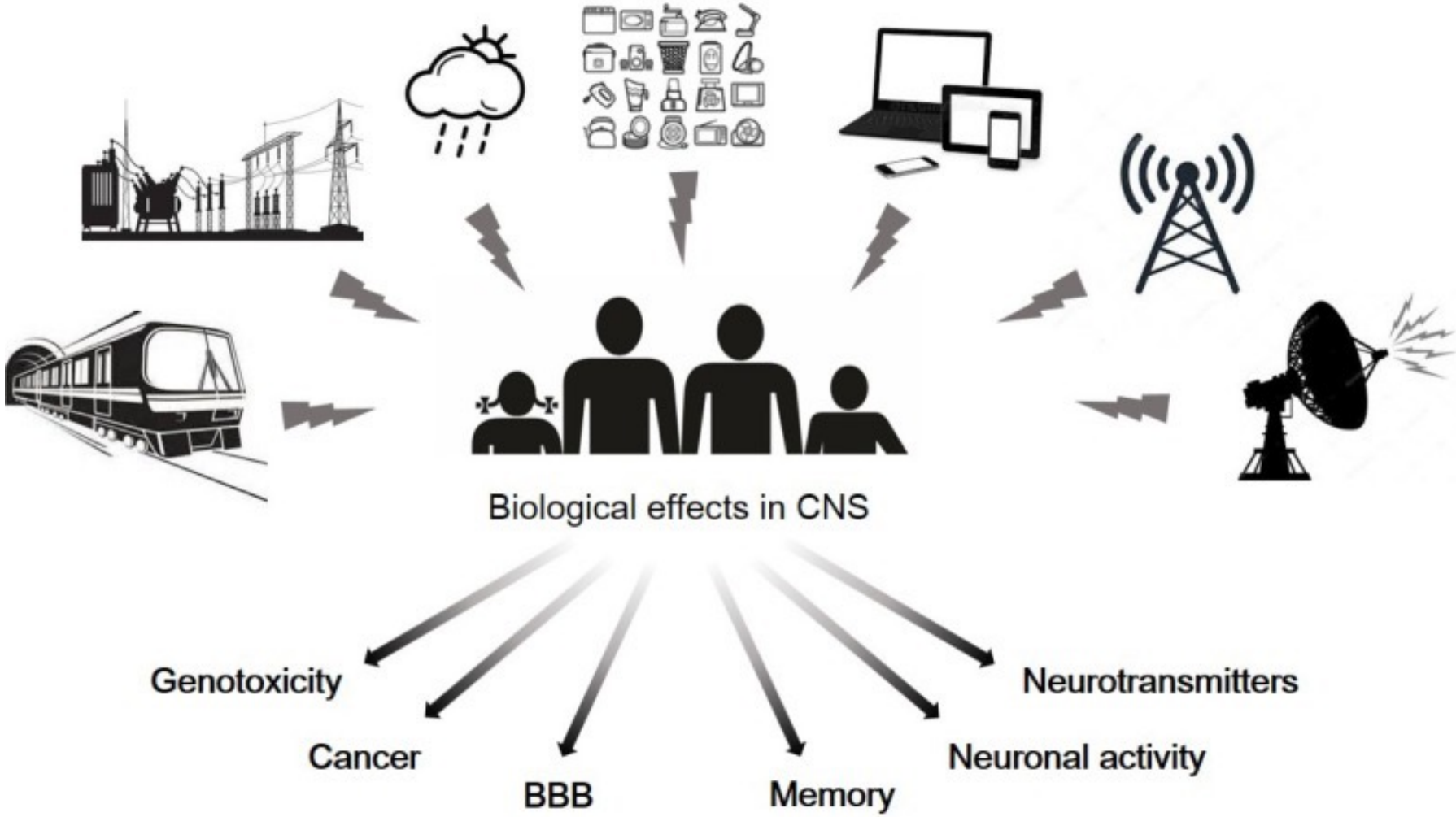
Role in synaptic plasticity which positively influences mood

Increases GABA in the brain

Nitrates increase production of BH4 increasing the production of neurotransmitters

BH4s Role in CV & Cognitive Health





Possible Effects of Radiofrequency Electromagnetic Field Exposure on Central Nerve System

2018 Nov 27. doi: 10.4062/biomolther.2018.152

NO & Cognition

High bp - risk factor for cognitive decline & dementia
Hypertension occurs decades prior to onset of dementia
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

Brain – 2% of body mass

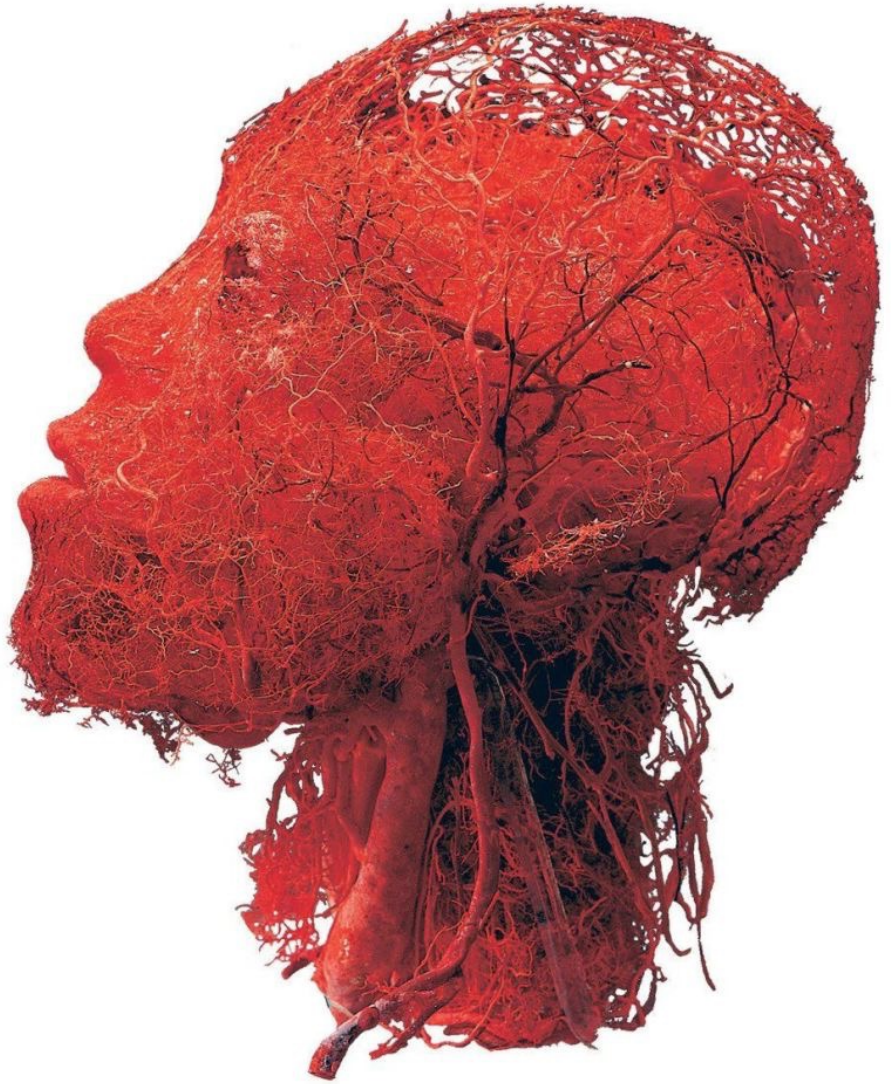
Consumes 20% of body's requirement for oxygen

Oxygen deficient – hypoxia

- Decreased ATP production aka decreased energy
- Mito become uncoupled
- Superoxide production increased

Cytochrome C oxidase - nitrite reductase enzyme

- Slows down oxygen consumption
- Increase NO production
- Improves microcirculation
- No decrease in ATP production



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

EMF & Learning, Memory & Cognition

VGCC – high density through nervous system

Increased ROS

Impairs BBB integrity

Neuroinflammation & neurodegeneration

Neuronal damage to cerebral cortex

Degenerative changes in cerebellum

Apoptosis of amygdala

Damages myelin sheath

Increased intracellular Ca2+ - disassembles cytoskeletal proteins, especially microtubules triggering apoptosis

Neurons - increased sensitivity to oxidative stress due to longevity and limited renewal

Manmade electromagnetic fields and oxidative stress – biological effects and consequences for health doi:10.3390/ijms22073772
Radiofrequency electromagnetic radiation-induced behavioral changes and their possible basis doi:10.1007/s11356-019-06278-5
Possible effects of radiofrequency electromagnetic field exposure on central nervous system doi.org/10.4062/biomolther.2018.15

EMF & Pain

VGCC – role in development of chronic pain

Increase Ca2+ into cell – triggers apoptosis or increased inflammatory cytokines

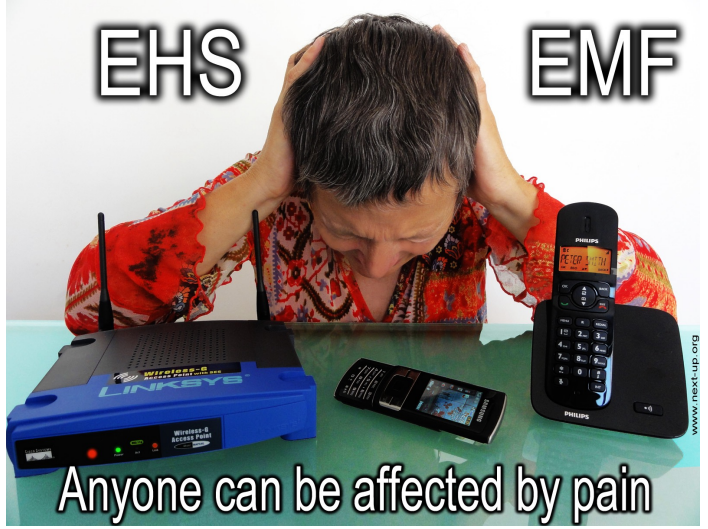
Inflammation causes pain and tissue damage

Subtypes of VGCC show abnormal functioning in persistent pain states

Activation of Ca2+ channels – glutamate, substance P

NMDA activation – major component of inflammatory, neuropathic pain

- CRPS
- Diabetic neuropathy



Role of calcium permeable channels in pain processing doi:10.5772/intechopen.77996

EMF & Pain

GABA reacts with VGCC & neuropathic pain
NO in brain inhibits GABA transamidase increasing GABA in brain
Compromised circulation – nerves malfunction
Lack of oxygen, nutrients & lower ATP affects membrane potential

NO downregulates neuronal transmission by inhibiting Ca2+ influx & activating K+ channels preventing action potential

Pain pathways blocked by morphine via NO, mediating relaxation response

Voltage-gated calcium and pain doi.org/10.1053/j.trap.2010.03.003
The role of endogenous morphine and nitric oxide in pain management. Practical Pain Management Vol 14 Issue 9 practicalpainmanagement.com

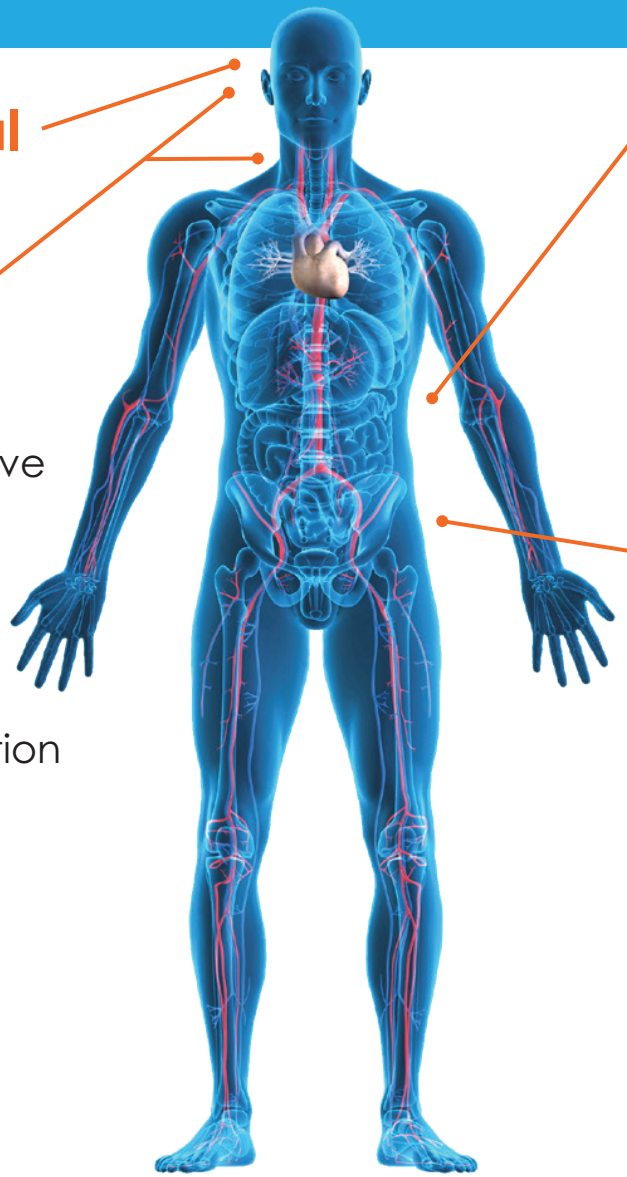
EMF Effects

Behavioral Psychological

- Anxiety/Depression
- ADD/OCD
- Stress/Emotional

Neurologic Effects

- Alzheimer's/Neurodegenerative diseases
- Cognitive dysfunction
- Learning/Memory
- Hypothalmic-Pituitary-Hormonal dysfunction
- Pineal/Thymus gland dysfunction
- Sleep disorders/Insomnia
- Brain tumors
- Tinnitus/Eye problems
- BBB disruption
- Microglial Inflammation
- Headaches



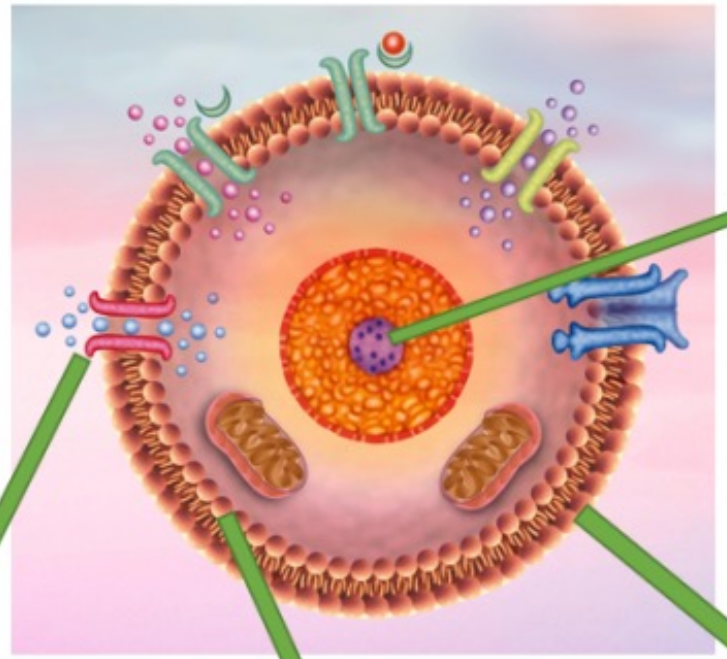
Immunological Effects

- Inflammation/Aging (Inflammaging)
- Imbalance (Th1/Treg–Th2/Th17 shift)
- Mast cell activation
- Stimulates pathogens
- Synergistic with toxins
- Autoimmunity

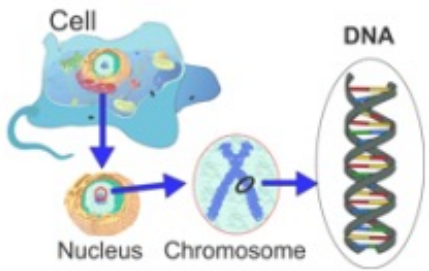
Cellular Effects

- Metabolic dysfunction/ Insulin resistance
- Mitochondrial dysfunction
- Cardiovascular dysfunction/HTN
- Fatigue/Weakness/Pain
- Cancers
- DNA damage/Epigenetic changes
- "Leaky gut"
- Infertility
- EMF sensitivity syndrome

4 MAIN PATHWAYS OF ELECTROMAGNETIC FIELD'S IMPACTING OUR CELLULAR HOMEOSTASIS



DNA



3. DNA acts as a fractal antenna reacting to exogeneous EM fields leading perturbation of the epigenetic code of genomes

C.C.V.D Oxydase

1. Calcium Voltage Gated Ion Channels respond to minus electric or electromagnetic stimuli (such as a cellular phone impulses)

MITOCHONDRIAL DNA

4. Mitochondria can be considered a « sub-unit » of cells, similarly, equipped with DNA and CCVD, thus also reactive to EMF exposure, with potential oxidation and inflammation processes by the production of R.O.S

NAPHD Oxydase

2. EMF excites membrane-bound enzymes on the extracellular surface o the cell called NADPH oxidase : it catalyzes the production of a superoxi free radical by transferring one electro to oxygen from NADPH

Source: www.biohacking.comosystems.com

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

EMF increases oxidative stress & increases free radicals
Damages membranes, cells & tissues – Altering physiological processes

Oxidative stress/Inflammation - plays role in Every Single chronic, degenerative, inflammatory condition

Oxidative stress uncouples NOS decreasing NO & increasing oxidative stress

NO inhibits Ca2+ influx regulating intracellular Ca2+ concentration modulating potential damage

NO is Base of health
Supporting nitrate/nitrite/NO pathway optimizes NO, increases NO directly, as well as recoupling NOS increasing NO, decreasing oxidative stress & inflammation

Thank You

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