Nitric Oxide and Hormones

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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, and super-normal oxidative stress.

Over the last eleven years, 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. She currently is the Executive Director of the Berkeley Life Scientific Advisory Board.
“Aging is the loss of hormones. Aging is the loss of nitric oxide.”
—Beth Shirley RPh CCN
Effects of Hormones on eNOS

Brain

Hypothalamus
Pituitary

LHRH

ACTH

Prolactin

LH
FSH

T/E₂

NOS → NO⁺/-

Thyroid

Liver

Pancreas

Ovaries

Testes

Adrenal

Glc

DHEA

T₃

T₄

GH

Insulin

Estrogen

Progesterone

Testosterone

Endothelial Cell

Effect on eNOS

NO

eNOS

Effect on eNOS
Nitric Oxide Pathways

The L-Arginine Pathway

L-arginine + O₂

NO synthase

NO

Biological effects

NO synthase

NO³⁻/NO₂⁻

The Nitrate Pathway

Diet

NO₃⁻

Bacterial nitrate reductases
Xanthine Oxidoreductase

NO₂⁻

Deoxygenated Hb, Mb
Xanthine Oxidoreductase
Respiratory chain enzymes
Protons

NO
So I can explain NOS Uncoupling.

**NOS Uncoupling**

Oxidative Stress
Diabetic Pathology
Lipid Peroxidation
BH₄ Status
Phosphorylation Status

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

“Uncoupled”
When NOS is uncoupled it produces Superoxide (O₂⁻) rather than nitric oxide (NO).
Nitric Oxide Decline

Progression of Endothelial Dysfunction

Nitric Oxide Decline with Age

% Decline in NO Production

Age in years

Progressive accumulation of fatty deposits
Stiffening of arteries
Plaque buildup
Nitrergic oxide
Inflammation
Calcium build up
100% Nitric oxide
80% Nitric oxide
70% Nitric oxide
60% Nitric oxide
50% Nitric oxide
Rupture (possible heart attack)

15% Nitric oxide
35% Nitric oxide
50% Nitric oxide
80% Nitric oxide
100% Nitric oxide

Progressive decline with age

men
women
## Current Factors Affecting NO Formation

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Effects of Hormones on eNOS
Nitric oxide regulates hormone release in the hypothalamic-pituitary axis.

Triggers pulsatile release of LHRH, which mediates LH release.
LH stimulates production of steroid hormones from testis (testosterone) and ovaries (estradiol).

**Estrogen stimulates eNOS to produce nitric oxide.**

**Estrogen** declines with age.
Results in decrease in eNOS function around menopause.
85% of women in the US are hypertensive by the age of 85.

**Progesterone** acts directly on epithelial cells of endometrium to stimulate expression of eNOS
Stimulates phosphorylation of eNOS to increase NO production

**Testosterone deficiency induces endothelial dysfunction.**
Deficiency can lead to erectile dysfunction and/or vascular dysfunction.
Regulates NO/cGMP pathway which directly influences endothelial function and endothelial progenitor cells (EPCs). EPCs are key for endothelial repair system.
Male Sexual Health

“ED is ED – Erectile Dysfunction is Endothelial Dysfunction”

Erectile Dysfunction is a general marker for CVD which affects:

- 20% of all adult males
- 30-50% of males between 40-70 years old
- More than 60% of men older than 70 years old

NO is a non-adrenergic non-cholinergic (NANC) neurotransmitter innervating penile corpus cavernosum.

NO plays a critical role in initiation of intracavernous pressure and penile erection and activates soluble guanyl cyclase to increase cGMP.

cGMP regulates activity of Ca++ channels to relax smooth muscles of the corpus cavernosum to allow engorgement.
Male Sexual Health

- **PDE5 Inhibitors** like Viagra and Cialis prolong the action of cGMP to extend erections. **THEY DO NOT CAUSE ERECTIONS**
  - Patients must have adequate nitric oxide in their tissue for those PDE5 Inhibitors to work.
  - Not effective in almost 50% of men treated.
- **Testosterone** has a dual action in tissue:
  1. Modulates NO/cGMP signaling mechanism by upregulating NOS expression increasing NO production
  2. Testosterone modulates PDE5 activity in penile tissue in regulating homeostatic mechanisms of penile erections.

**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 cardiovascular complications.**
Female Sexual Health

Research shows that in the US, between 25-60% of women experience some sort of sexual dysfunction.

—Female genital arousal response is all mediated by Nitric Oxide—

Sexual arousal encompasses a variety of physiological responses mediated by NO that includes:

• Potent vasodilator of clitoral, labial and vaginal tissue
• NANC neurotransmitter in clitoral corpus cavernosum to relax smooth muscles, as in males, to increase blood flow and response
• Increased blood flow means better orgasms
• Decreases anxiety which increases sexual pleasure
Nitric Oxide plays the following roles:

- Neurotransmitter in the brain which modulates the release of oxytocin and LHRH – both central in modulation of sexual behavior
  - Oxytocin (cuddle hormone, love hormone) increases NO through NOS and in turn, orgasms increase oxytocin
- Involved in creation of long-term memory.
- Studies show that memory and libido are closely connected.
- Enhances ability to remember sex scents (pheromones)
- Following sexual stimulation, NO modulates release of 3-5ml vaginal transudate to enhance lubrication

SSRIs inhibit NOS, decreasing NO production and blocking arousal in both men and women. Can lead to problems with desire, arousal, ejaculation in men and orgasm.
Stress initiates the fight/flight/freeze response, while non-essential functions, like sex drive, reproduction, and digestion are acutely diminished.

**Adrenals require adequate NO to work effectively**

**Glucocorticoid** production in adrenal glands is increased in absence of NO.

**Cortisol** is the only hormone that naturally increases with age:

- Inhibits both iNOS and eNOS
- Increases ROS in mitochondria, NADPH oxidase (NOX) and xanthine oxidase
- Decreases synthesis of BH4 which increases NOS uncoupling
- Decreases membrane transport of l-arginine

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

**DHEA**: prohormone which metabolizes into other estrogens and testosterone.

Synthesized in the adrenal cortex, gonads, adipose tissue, brain and skin directly increases NO production by the activation of eNOS.

Low DHEA levels are associated with higher risk of ED in men and low sexual responsiveness in women.
Pituitary Gland

Growth Hormone (GH) and IGF1 stimulate eNOS.
- Adult hypo-pituitarism and untreated GH deficiency is associated with endothelial dysfunction, decreased NO production, increased peripheral resistance and increased cardiovascular mortality and morbidity.

Oxytocin (Love Hormone) affects sexual health.
- Oxytocin induces penile erection by increasing NOS activity in the cell bodies of oxytocinergic neurons, projecting to extra-hypothalamic brain areas and mediating the behavioral responses.
- Increases NO production through NOS and levels are greatly increased after orgasm.

Nitric Oxide could extend fertility.
- NO appears to slow or reverse the aging of eggs in mouse ovaries. Suggests NO may help women in their 30s and 40s remain fertile longer and increase their chances of having healthy babies.
Metabolic System

NO regulates carbohydrate metabolism and insulin production. Emerging as a central regulator of energy metabolism and body composition. Impairment of NO synthesis is a central defect causing metabolic abnormalities associated with insulin resistance.

**Insulin initially stimulates eNOS activity, essential for endothelial NO production**

**Insulin resistance** decreases eNOS phosphorylation which increases NOS uncoupling and causes:
- Loss of endothelial function
- Increased expression of vascular cell adhesion molecule 1 (VCAM 1) and other adhesion molecules increasing cardiovascular complications.

**GLUT 4 receptor** requires adequate NO in order to translocate and bring glucose into the cell.

**HbA1C** binds tightly with NO rendering NO not bio-available.

**NOS pathway is impaired with blood sugar dysregulations and oxidative stress in a way that the Nitrate to Nitrite to NO pathway is not.**
Polycystic Ovarian Syndrome (PCOS) is related to insulin resistance, diabetes, obesity, oxidative stress, inflammation, and cardiovascular disease. All of these conditions are mediated by NO. Increased oxidative stress increases NOS uncoupling.

- Decreases T-reg cells which modulate the immune system, maintain tolerance to self antigens and prevent autoimmune disease. All regulated by NO

- Increases ADMA (asymmetric dimethyl arginine)
  - Decreased arginine bioavailability.
  - Competes with arginine in the NOS enzyme and uncouples NOS.
  - ADMA plasma levels predicts all causes of mortality

Birth Control pills uncouple NOS, decreasing the production of NO and increasing the oxidative stress.
Thyroid

NO deficiency expressed as cold extremities in thyroid disorders.

NADPH oxidase (NOX) enzymes in thyroid are called DUOX1 and DUOX2. Increase ROS (reactive oxygen species), superoxide and hydrogen peroxide.

Important – precise amounts of H2O2 is required for thyroid peroxidase (TPO). Increased DUOX activity along with decreased TPO activity has deleterious effects on the thyroid tissues caused by oxidative stress.

Several factors such as environmental toxicities, mold exposure, mast cell activation, stress, chronic infections or inflammation contribute to the upregulation of NOX and DUOX, which increases ROS. Oxidative stress downregulates the production of NO.

NO and nitrates inhibit NOX and DUOX enzymes.

Supporting the nitrate to nitrite to NO pathway may be an underutilized thyroid therapy due to its role in decreasing the production of superoxide and other ROS by optimizing NO levels, scavenging ROS, and supporting healthy circulation and microcirculation.
REM sleep plays a significant role in maintaining emotional well-being and psychological balance. NO regulates the release of acetylcholine and consequently the occurrence of REM sleep.

Homeostatic regulation of REM sleep is an age-dependent process involving NO. When we lose the ability to produce adequate NO, sleep becomes disturbed.

Reduced NO production contributes to age-associated impairment of clock gene expression. Basically, impairment of NO production results in a phase shift of the circadian clock. When circadian rhythmicity is impaired, a condition called non-dipper hypertension can occur.

Decreased NO from aging is linked to impaired circadian rhythm.
Anxiety and Depression

• NO may be involved in the regulation of anxiety like behavior. Anxiety and depression are associated with low levels of BDNF
• NO:
  • mediates the neuroprotective actions of BDNF in promoting neuronal survival and stimulating the process of neurogenesis.
  • induces neurogenesis, enhances learning and memory
  • plays a role in synaptic plasticity which positively influences mood
• Nitrates increase production of BH4 increasing the production of neurotransmitters.

Supporting the nitrate to nitrite to NO pathway will decrease oxidative stress and inflammation.

Oxidative stress and inflammation play a huge role in biological dysfunction everywhere and anywhere.
The Affect of Nitrates of Oxidative Stress

Mechanisms of the protective effects of nitrate and nitrite in cardiovascular and metabolic diseases.

Dietary Nitrate → Nitrosation → S-nitrosothiols → Complex I activity → ROS

Nitrite → Non-enzymatic and enzymatic pathways → Peroxynitrite production

→ NO bioavailability and bioactivity

→ Tetrahydropterin (BH4) Consumption

*Mechanisms of the protective effects of nitrate and nitrite in cardiovascular and metabolic diseases.

Nitric Oxide. doi:10.1016/j.niox.2020.01.006
Summary

NO production naturally declines with age, reducing to 50% by the time we are 40 and up as little as 15% by the time we are 60.

NO and Hormones are intricately intwined to keep circulation and microcirculation healthy, cells and tissues supplied with oxygen, glucose and nutrients combined with the cellular debris carried away for optimal health.

Supporting the nitrate to nitrite to NO pathway not only increases NO directly, it helps recouple NOS to increase NO through that pathway decreasing oxidative stress.

Aging is the loss of Hormones.
Aging is the loss of Nitric Oxide.
Hormones References

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