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Longevity and Biological Ageing: Enhancing Health into Advanced Age



SESSION 8

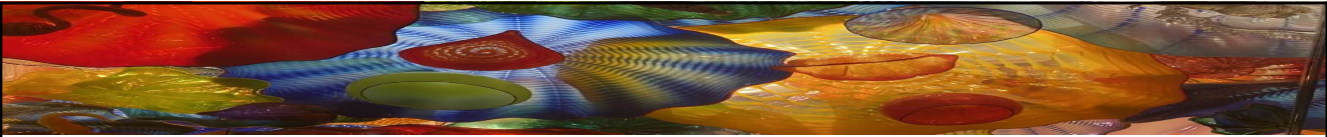
Dr. Felice Gersh

Women’s Health from Menarche through Menopause:
An Integrative Approach to Optimisation of Mitochondrial
Function

9:30-10:30am

An event by:  Nutritional Medicine
Institute

Platinum sponsors:   regenerus labs



Women's Health from Menarche through Menopause: An Integrative Approach to Optimisation of Mitochondrial Function

**Felice Gersh MD
Medical Director
Integrative Medical Group of Irvine
Affiliate Faculty
Fellowship in Integrative Medicine University of
Arizona School of Medicine**



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Disclosures

- Nestle Health Sciences – Lecturer/Educator
- Soleria Bio – Lecturer/Educator
- Metagenics – Lecturer/Educator
- WonderFeel – Lecturer/Educator
- L-Nutra – Lecturer/Educator

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Objectives

- Review lesser-known elements of puberty
- Understand the role of mitochondria and ovarian function – menarche to menopause
- Itemize the important health manifestations of perimenopause and menopause and their functional medicine correlates
- Develop an integrative and functional medicine therapeutic approach to healthy ovarian function, perimenopause, and menopause

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**How Can We View These
Myriad Stage of Life:
Menarche/Perimenopause/Menopause**

**Through the Lense of Life Itself -
By Acknowledging the
Prime Directive of Life**



6

**Prime Directive of Life:
Reproduction and Survival**

***and then to repeat the
process ...
And for new life —
it all begins while in the uterus
and proceeds with puberty***

**It's all about the
process of making
and raising babies!**



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**REPRODUCTION & SURVIVAL
REQUIRES HORMONES!
WOMEN'S OPTIMAL HEALTH =
OPTIMIZED HORMONES**

**MAKING HORMONES
REQUIRES A LOT OF ENERGY!**

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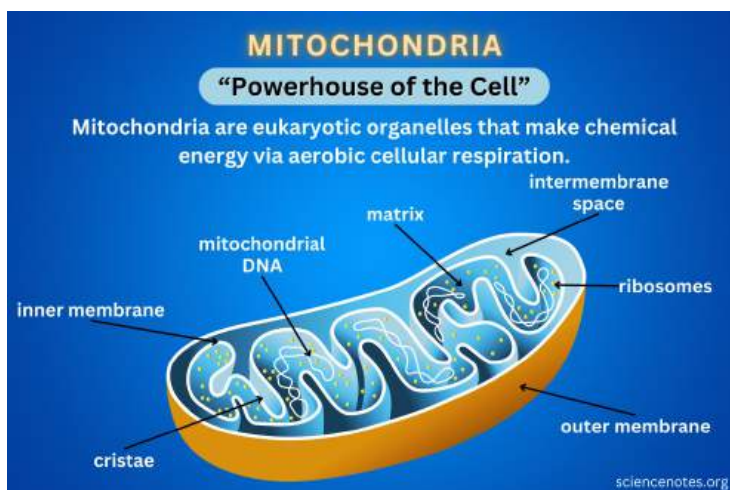
Optimal Hormone Production and Function Requires Lots of Energy - for Puberty

- Relationship between puberty and mitochondria - two-way street: mitochondria provide essential energy for rapid growth and hormonal changes of adolescence & onset of puberty triggers significant shifts in their function in different tissues
- Puberty triggers major mitochondrial maturation - changes in number, structure, and activity (specifically in oxidative phosphorylation) - supports rapid growth and reproductive development - Estrogen boosts mitochondrial biogenesis
- Dysfunction in mitochondria - early puberty or impaired growth

Abreu AP, Kaiser UB. Pubertal development and regulation. *Lancet Diabetes Endocrinol.* 2016 Mar;4(3):254-264. doi: 10.1016/S2213-8587(15)00418-0. Epub 2016 Feb 4.

9

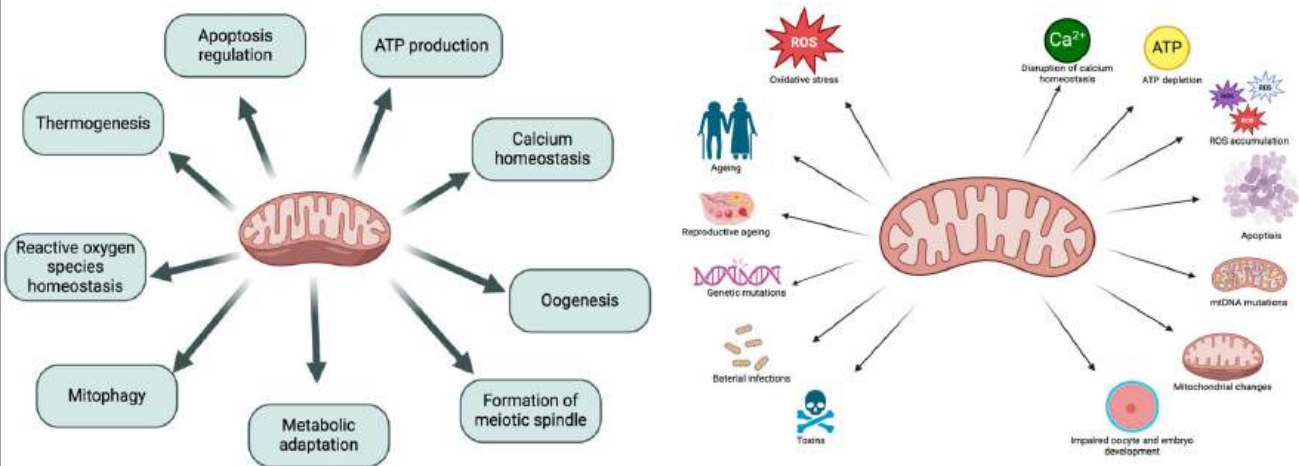
We Can Think of a Female Life as a Journey Through Energy Challenges and Changes



- Mitochondria: rod-shaped, double-membrane organelles
- The “powerhouse of cells”
- Parts:
Outer membrane
Highly folded inner mitochondrial membrane (cristae)
Intermembrane space
Internal gel-like matrix
- These components are crucial for aerobic respiration and ATP production

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Take a Step Back: Introducing Mitochondria: Normal & Abnormal Mitochondria



Gałęska E, Kowalczyk A, Wrzecińska M, Garcia MC, Czerniawska-Piątkowska E, Gwoździwicz S, Witkiewicz W, Dobrzański Z. The Importance of Mitochondrial Processes in the Maturation and Acquisition of Competences of Oocytes and Embryo Culture. *Int J Mol Sci.* 2025 Apr 25;26(9):4098.

11

Mitochondrial Basics

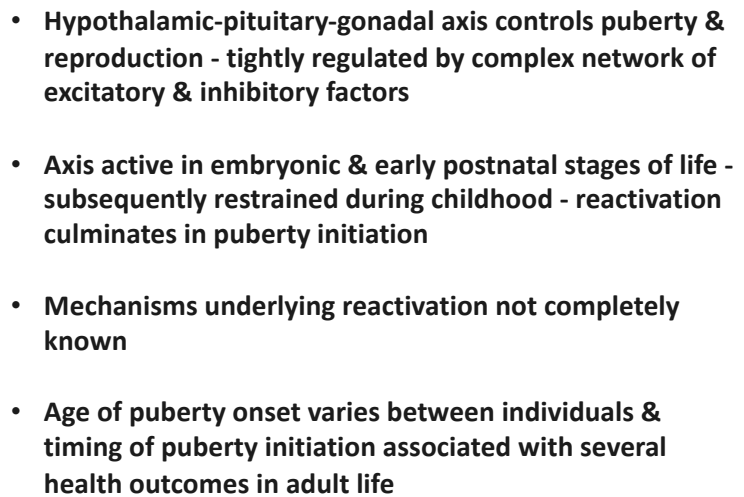
>40% of mitochondrial proteins are linked to human diseases, underscoring the centrality of mitochondria to human health

- Energy metabolism
- Aging process – the cell cycle
- Regulation of homeostasis
- Associated with neurodegenerative disease
- Genetic Syndromes
- Oxidative phosphorylation
- Beta oxidation
- Heme biosynthesis
- Calcium buffering
- Steroidogenesis
- Apoptosis signaling

Anu Suomalainen, Jodi Nunnari, Mitochondria at the crossroads of health and disease, *Cell*, Volume 187, Issue 11, 2024, Pages 2601-2627, ISSN 0092-8674

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Puberty marks end of childhood & beginning of physiological & psychological changes to achieve sexual maturation & fertility



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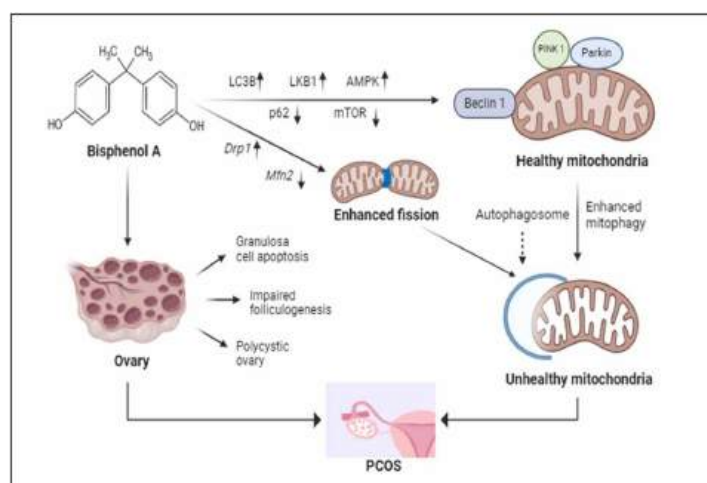
14

Pubarche (Adrenarche) Begins

- Development axillary and pubic hair - process termed pubarche - not be used as marker of onset of puberty
- Pubarche dependent on increase in adrenal androgen production - physiological event termed adrenarche
- Serum concentration of dehydroepiandrosterone sulphate (DHEAS) is best marker for presence of adrenarche - begins about age 6 years - several years before activation of hypothalamic-pituitary-gonadal axis (gonadarche)
- Although development of axillary and pubic hair requires adrenarchal concentrations of androgen, clinically evident pubarche does not usually appear until shortly after physical evidence of gonadarche - breast development in girls

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BPA-Induced Oxidative Stress Leading to Mitochondrial DNA Mutations and its Subsequent Implications on the Ovary



Abbreviations- mtDNA: Mitochondrial DNA ROS: Reactive oxygen species; TAC: Total antioxidant capacity

Reproductive Toxicology
Volume 130, December 2024, 108700

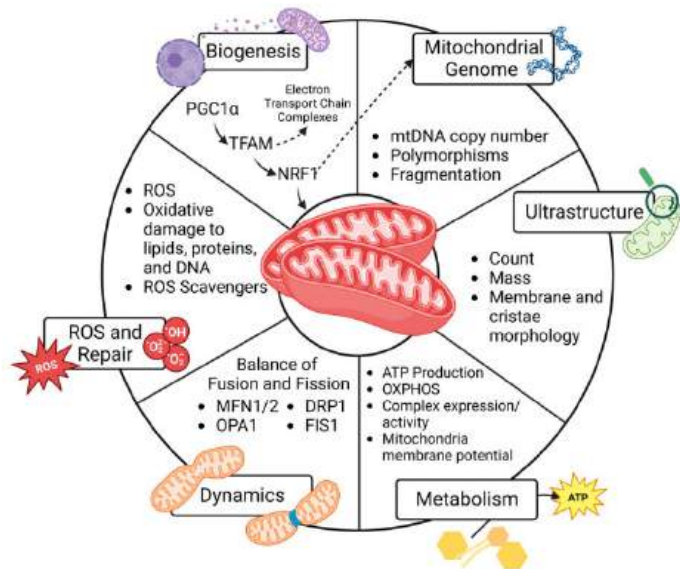
Review

Altered mitochondrial homeostasis on bisphenol-A exposure and its association in developing polycystic ovary syndrome: A comprehensive review

Supraja M. Kodanch^a, Sayantani Mukherjee^a,
Navya B. Prabhu^a, Shama Prasada Kabekkodu^b,
Shashikala K. Bhat^c, Padmalatha S. Rai^a

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Review: Key elements that regulate mitochondria number and function to influence cell processes and fate



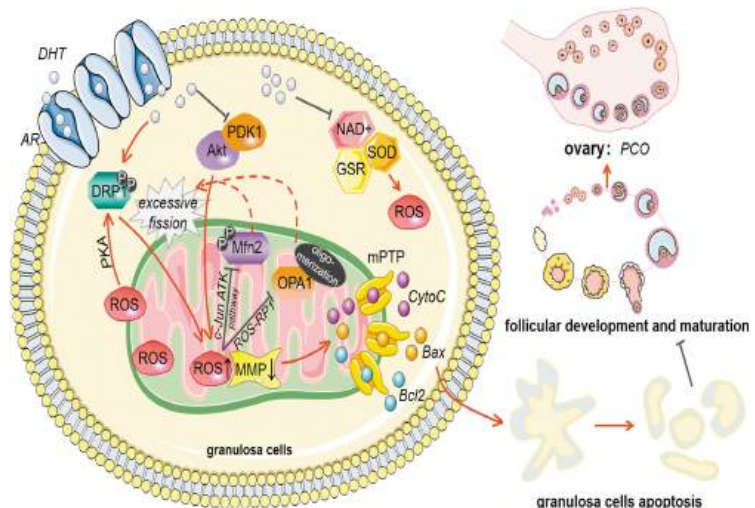
Siemers KM, Klein AK, Baack ML. Mitochondrial Dysfunction in PCOS: Insights into Reproductive Organ Pathophysiology. *Int J Mol Sci.* 2023 Aug 23;24(17):13123.

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Mitochondrial Dysfunction and Granulosa Cells

Mitochondria important for:

- Metabolism, growth, & differentiation of GCs
- Play crucial role in follicular development and maturation & in pathogenesis of the disease
- Androgen (e.g. DHT) important factor affecting physiological function of GCs

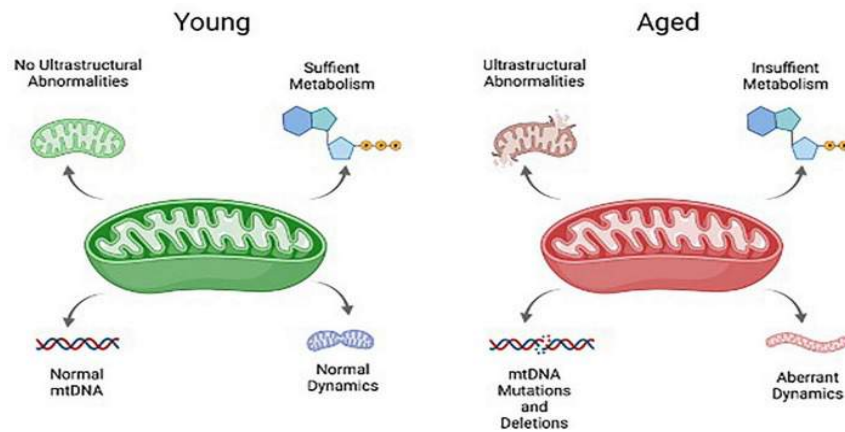


c-Jun ATK pathway, c-Jun amino-terminal kinase pathway; DHT, dihydrotestosterone; GC, granulosa cell; ROS-RP1, reactive oxygen species regulatory protein 1

Sun C, Zhao S, Pan Z, Li J, Wang Y, Kuang H. The Role Played by Mitochondria in Polycystic Ovary Syndrome. *DNA and Cell Biology.* 2024;43(4):158-174.

20

Mitochondrial Aging: Negatively impacted by aging (Hormone Deficiency)



mtDNA, mitochondrial ultrastructure & integrity, metabolism, mitochondrial dynamic

21

Mitochondrial Impacts on Many Female Reproductive Conditions



► Antioxidants (Basel). 2020 Oct 15;9(10):994. doi:
[10.3390/antiox9100994](https://doi.org/10.3390/antiox9100994)

Primary Dysmenorrhea in Relation to Oxidative Stress and Antioxidant Status: A Systematic Review of Case-Control Studies

[Maria Karolina Szmidt](#)^{1,*}, [Dominika Granda](#)¹, [Ewa
Sicinska](#)¹, [Joanna Kaluza](#)¹



Review 3 July 2025

The Role of Mitochondrial Dysfunction and Oxidative Stress in Women's Reproductive Disorders: Implications for Polycystic Ovary Syndrome and Preeclampsia

[Evangeline Deer](#), [Babbette LaMarca](#)^{*},
[Jane F. Reckelhoff](#), [Noha M. Shawky](#) and
[Kristin Edwards](#)

Department of Pharmacology and Toxicology,
Women's Health Research Center, Mississippi
Center of Excellence in Perinatal Research,
University of Mississippi Medical Center, Jackson,
MS 39216, USA

^{*} Author to whom correspondence should be
addressed.

Int. J. Mol. Sci.
2025, *26*(13), 6439;
<https://doi.org/10.3390/ijms26136439>

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Mitochondrial Impacts on Many Female Reproductive Conditions

Highlights

- Impaired mitochondrial biogenesis and dynamics contribute to disease progression.
- Altered mitophagy leads to accumulation of dysfunctional mitochondria in endometriosis.
- Mitochondrial dysfunction impacts inflammation, apoptosis, and cell cycle control, offering targets for new treatments.
- Circadian rhythm influences mitochondrial dynamics and consequently the progression of endometriosis.
- Estrogen receptors and the microbiome are involved in the exacerbation of endometriosis.

Biochimie

Volume 231, April 2025, Pages 163-175

Mitochondrial dynamics: Molecular mechanism and implications in endometriosis

Ylenia Marino ^a✉, Francesca Infrerra ^a✉, Tiziana Genovese ^a✉, Salvatore Cuzzocrea ^{a,c}✉, Roberta Fusco ^a✉, Rosanna Di Paola ^b✉

Mitochondrial Impacts on Many Female Reproductive Conditions

The American Journal of Pathology

Volume 195, Issue 5, May 2025, Pages 861-874

Regular article

Epithelial and Mesenchymal Cell Biology

The Involvement of Mitochondrial Dysfunction during the Development of Adenomyosis

Nari Kay ^{*}, Chun-Yen Huang ^{*†}, Ya-Chun Yu ^{*†}, Chih-Chen Chen ^{*}, Chi-Chang Chang ^{#‡}, S. Joseph Huang ^{*‡§¶}✉

Oxidative Medicine and Cellular Longevity

• Oxid Med Cell Longev. 2022 Jul 13;2022:3599246. doi: [10.1155/2022/3599246](https://doi.org/10.1155/2022/3599246)

Role of Inflammation, Oxidative Stress, and Mitochondrial Changes in Premenstrual Psychosomatic Behavioral Symptoms with Anti-Inflammatory, Antioxidant Herbs, and Nutritional Supplements

Arshiya Sultana ^{1,¶¶}, Khaleesur Rahman ², Md Belal Bin Heyat ^{3,¶¶}, Sumbul ¹, Fajjan Akhtar ⁴, Abdullah Y. Muad ^{5,¶¶}

Obstetrics & Gynaecology

Journal of Obstetrics and Gynaecology Research / Volume 49, Issue 12 / pp. 2783-2791

Review Article

The role of mitochondrial dynamics in the pathophysiology of endometriosis

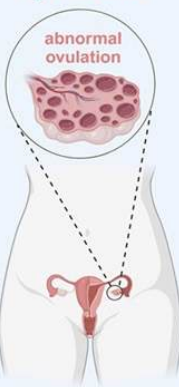
Hiroshi Kobayashi [✉], Sho Matsubara, Chiharu Yoshimoto, Hiroshi Shigetomi, Shogo Imanaka

First published: 08 September 2023
<https://doi.org/10.1111/jog.15791>

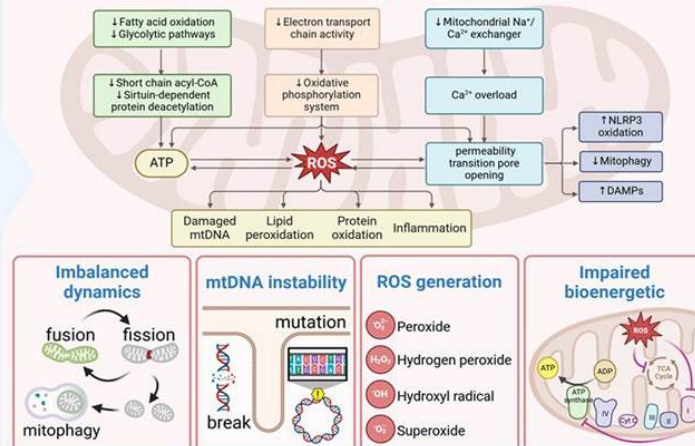
Graphical abstract

Unraveling Mitochondrial Dysfunction in Polycystic Ovary Syndrome: Pathophysiological Insights

Polycystic Ovary Syndrome



Mitochondrial dysfunction

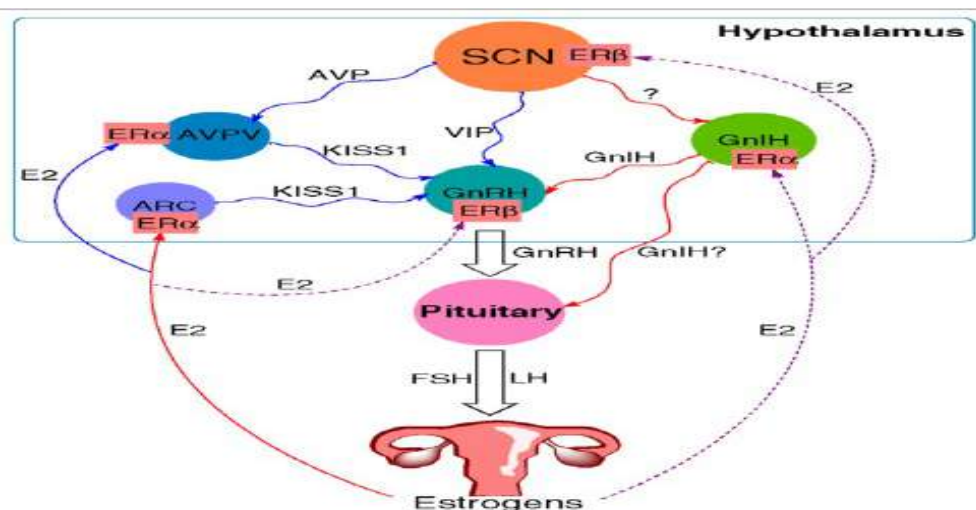


ATP= Adenosine Triphosphate; ROS= Reactive Oxygen Species; mtDNA= Mitochondrial DNA; DAMPs= Damage-Associated Molecular Patterns; TCA Cycle=Tricarboxylic Acid Cycle; Cyt c=Cytochrome c

Li CJ et al. | Journal of the Chinese Medical Association (JCMA) | 2025; 88:(11).

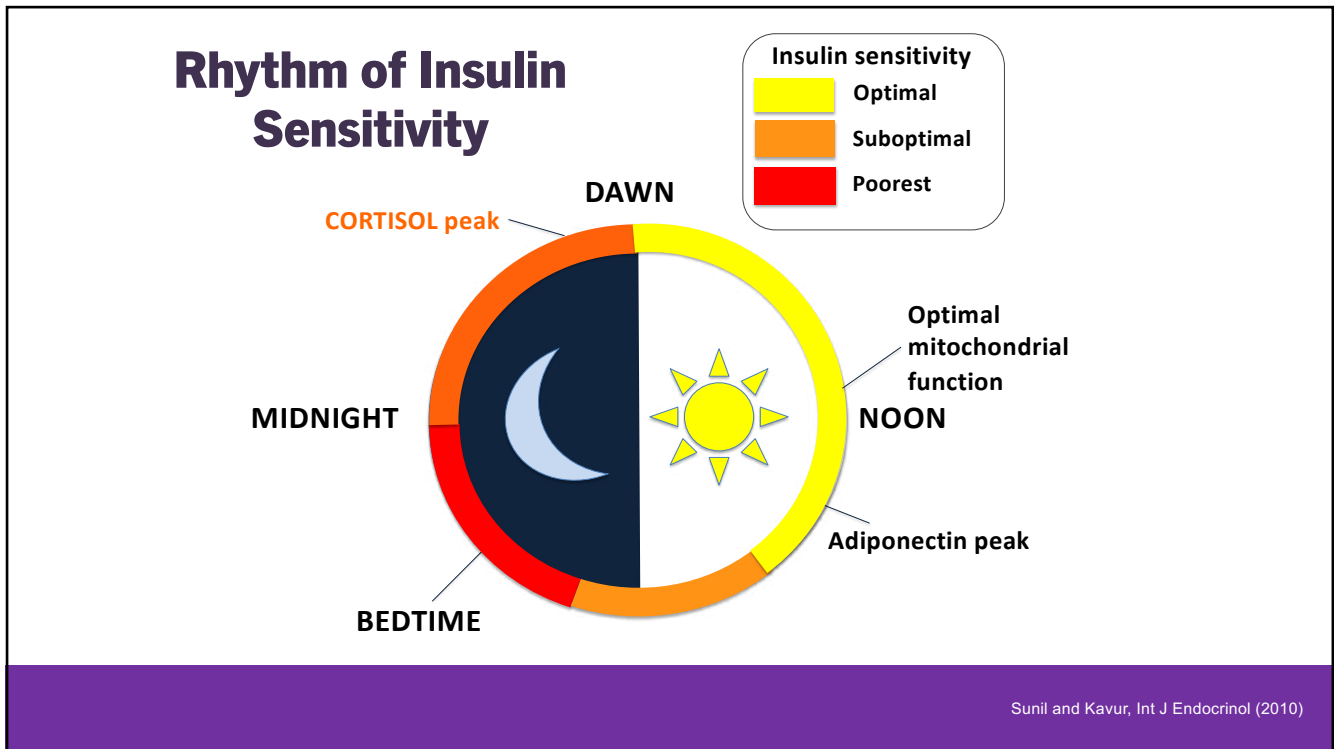
25

Estradiol – Reproduction – Metabolism & Circadian Rhythm



Royston et al. Endocrinology. 2014;155(7):2613-23
Unlep et al. Front. Endocrinol. 2013. 00111

26



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Impact of 8 Days of Circadian Disruption

Eating and sleeping 12 hours earlier or later than habitual times

- “Flipped” daily cortisol rhythm
- Decreased leptin (-17%)
- Increased insulin (+22%)
- Reduced sleep efficiency (-20%)

Scheer et al., PNAS 2009;106(11):4453-8

28

Gut Microbiome Clock

Programmed to anticipate food in the daytime only

Bacteria express circadian patterns of swarming & motility



Marquie et al. Occup Environ Med. 2015;72(4):258-64
Castanon-Cervantes et al. 2010. J of Immunol; 185(10):5796-5805
Liang et al. 2015; Proceedings of Nat Acad of Sciences of the USA: 112(33); 10479-10484
Bechtold et al. 2010; Trends in Phar Scie, 31(5):191-8

29

Targeted Supplements

Vitamin D Prenatal Vitamin	Magnesium	Probiotic	Omega 3
Chastetree	Myo-inositol	NAC	Berberine
Ubiquinol	Zinc	NMN/NR	Oil of Evening Primrose



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Medicine

HomeSearchBrowse & Reference

► *Medicine* (Baltimore). 2020 Nov 13;99(46):e23130.
doi: [10.1097/MD.00000000000023130](https://doi.org/10.1097/MD.00000000000023130)

Efficacy of coenzyme Q10 supplementation on glucose metabolism, lipid profiles, and biomarkers of inflammation in women with polycystic ovary syndrome

A protocol for a systematic review and meta-analysis

[Min Liu](#)^a, [Hongqiu Zhu](#)^{b,*}, [Xiaodan Hu](#)^a, [Ying Zhu](#)^a,
[Haiyan Chen](#)^a

Review

Efficacy and Safety of Coenzyme Q10 Supplementation in the Treatment of Polycystic Ovary Syndrome: a Systematic Review and Meta-analysis

Tianqing Zhang et al. *Reprod Sci.* 2023 Apr.

31

Randomized Controlled Trial

The Effects of Magnesium and Zinc Co-Supplementation on Biomarkers of Inflammation and Oxidative Stress, and Gene Expression Related to Inflammation in Polycystic Ovary Syndrome: a Randomized Controlled Clinical Trial

Faraneh Afshar Ebrahimi et al. *Biol Trace Elem Res.* 2018 Aug.

Overall, magnesium and zinc co-supplementation, compared with the placebo, for 12 weeks among PCOS women had beneficial effects on serum hs-CRP, plasma PCO, TAC, and gene expression of IL-1 and TNF-α.

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SYSTEMATIC REVIEW article

Front. Nutr., 28 September 2023
Sec. Nutrition and Metabolism
Volume 10 - 2023 |
<https://doi.org/10.3389/fnut.2023.1209614>

This article is part of the Research Topic
A New Era: Shaping Women's Metabolic
Health, Fertility, and Sex-Related Cancers

[View all 10 articles >](#)

**The effects of N-acetylcysteine
supplement on metabolic
parameters in women with
polycystic ovary syndrome: a
systematic review and meta-analysis**

 Jiajun Liu^{1,2}  Haodong Su^{1,2}
 Xueshan Jin³  Lan Wang^{1,2}

Conclusion: This study suggests that NAC is effective in improving metabolic parameters in PCOS and may be a promising nutritional supplement for the treatment of PCOS.

► [Ann Med Surg \(Lond\)](#). 2023 Jun 5;85(7):[3506–3511](#).
doi: [10.1097/MS9.0000000000000879](#) 

Vitamin D and polycystic ovary syndrome (PCOS): a review

[Anmol Mohan](#)^a, [Ramsha Haider](#)^a, [Hajar Fakhor](#)^e,
[Fnu Hina](#)^d, [Vikash Kumar](#)^f, [Aleeza Jawed](#)^b, [Koushik](#)
[Majumder](#)^{h,*}, [Aliza Ayaz](#)^a, [Priyanka Mohan Lal](#)
[Usha Tejwaney](#)^g, [Nanik Ram](#)^c, [Saka Kazeem](#)^f

Highlights

- The paper discusses the prevalence of Vitamin D deficiency in women with polycystic ovary syndrome (PCOS) and the potential impact of Vitamin D supplementation on symptoms of PCOS.
- The paper highlights the potential link between Vitamin D deficiency and the development and progression of PCOS, with low Vitamin D levels potentially contributing to insulin resistance and inflammation, which are hallmark features of PCOS.
- The paper highlights that Vitamin D supplementation may help improve symptoms of PCOS, including menstrual irregularities, hirsutism, and insulin resistance.

► Life (Basel). 2023 Jan 2;13(1):125. doi:
[10.3390/life13010125](https://doi.org/10.3390/life13010125)

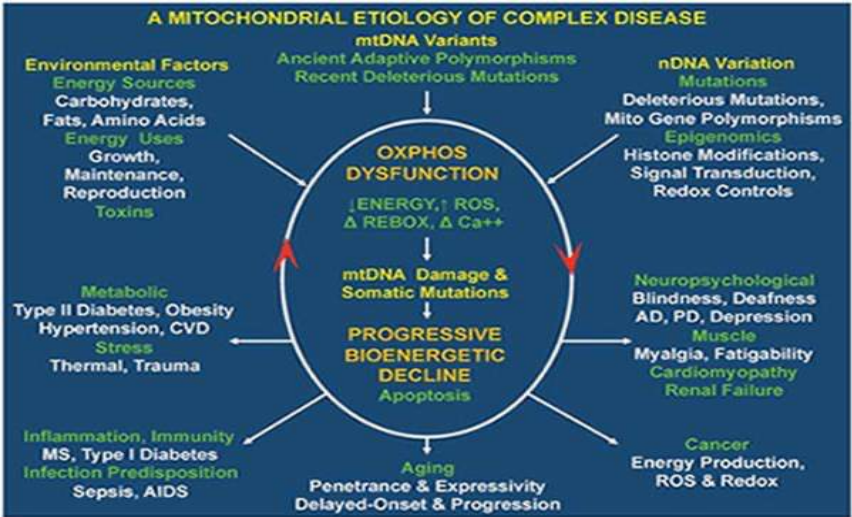
**Berberine—A Promising
Therapeutic Approach to
Polycystic Ovary Syndrome in
Infertile/Pregnant Women**

[Oana-Maria Ionescu](#)¹, [Francesca Frincu](#)^{1,*}, [And
Mehedintu](#)¹, [Mihaela Plotogea](#)², [Monica Cirstoiu](#)
[Aida Petca](#)¹, [Valentin Varlas](#)¹, [Claudia Mehedi](#)

There is encouraging evidence of superior effect of berberine alone vs. placebo/no regimen regarding the live birth rate, ovulation rate, androgen levels, decreasing fasting plasma glucose, and insulin levels, as well as the lowering of insulin resistance.

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**Back to Mitochondria:
A Mitochondrial Etiology of Complex Disease**



Wallace DC. Bioenergetic origins of complexity and disease. Cold Spring Harb Symp Quant Biol. 2011;76:1-16. doi: 10.1101/sqb.2011.76.010462.

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**Menopause is not
just the loss of
fertility and
periods...**

**It is the beginning
of a major metabolic
shift in mitochondrial
function**

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Menopause Affects All Organ Systems Including:

Immune Health

Brain Health

Cardiovascular Health

Sexual/Genito-Urinary Health

Bone Health

Skin Health



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The Many Health Consequences of Menopause

Estrogen receptors are everywhere and play vital roles in regulating countless physiologic functions: all involve mitochondria

- Cardiovascular Health
- Obesity & Increased Visceral Fat
- Metabolic Syndrome & Diabetes
- Musculoskeletal effects, Osteoporosis & Osteoarthritis
- Alzheimer's Disease & Neuro-inflammation
- Cancer (breast, colon)
- Autoimmune disease
- Fatty Liver (fatty other organs)
- GI Disorders: GERD, Malabsorption & Motility

Adapted from Exper Rev Endocrinol Metab© 2011 Expert Reviews Ltd

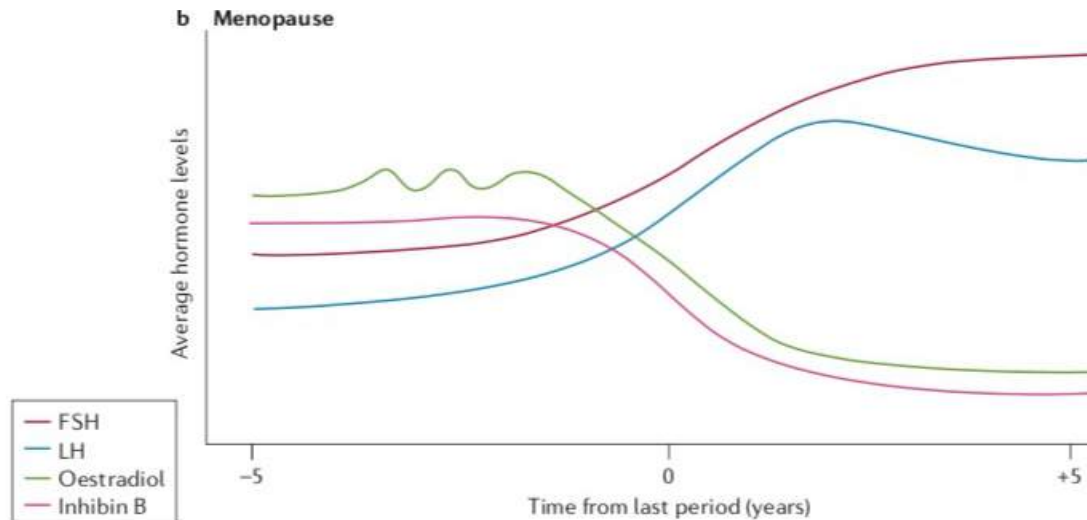
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Estrogen Basics: Estrogens are a Family of Hormones — Always use Estradiol



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Menopausal Hormones: Transition and Thereafter



Davis, S., Lambrinoudaki, I., Lumsden, M. *et al.* Menopause. *Nat Rev Dis Primers* 1, 15004 (2015).

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Modulated by Estradiol:

Vasodilation and vasoconstriction

- Endothelial NO synthase
- Prostacyclin cyclooxygenase
- Prostacyclin synthase
- Renin and angiotensin
- Endothelin-1

Lipid Metabolism

- Lipoprotein lipase
- Apo-lipoproteins
- Leptin
- PON 1
- LDL receptors
- HMG-CoAR activity

Immune activity

- Vascular-cell adhesion molecule
- Cytokines (IL1, IL6, TNF α)
- Cytokine receptors
- Superoxide Dismutase

Coagulation

- Fibrinogen
- Coagulation factors, Protein S

Angiogenesis

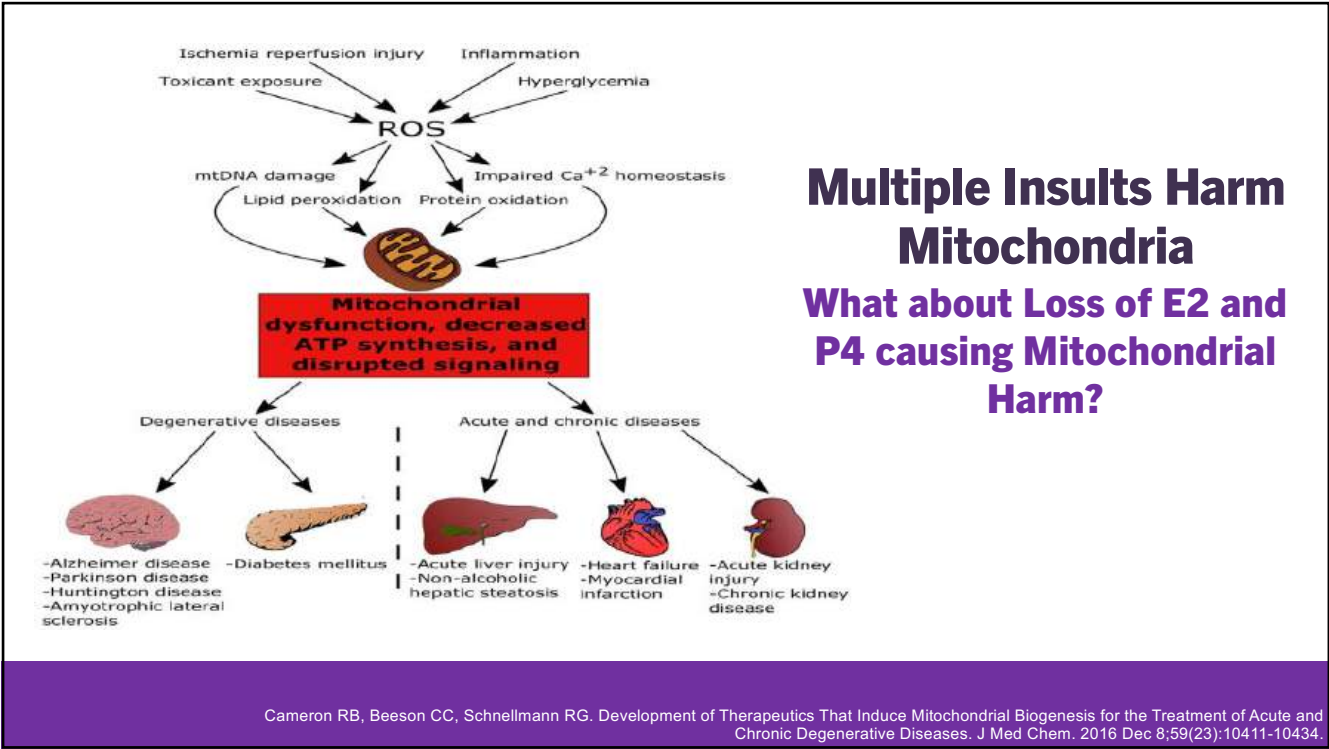
- Matrix metalloproteinase
- Vascular endothelial growth factor

Non-Genomic Effects

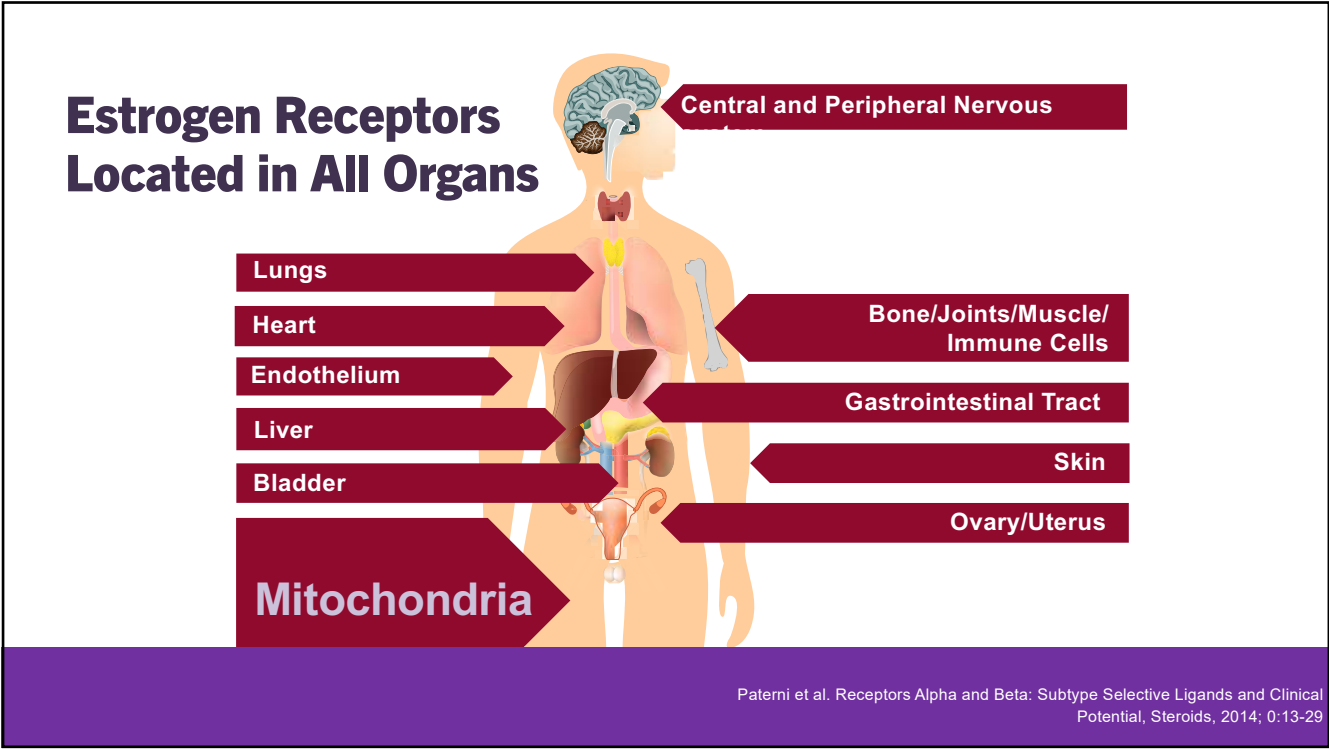
- Fast-acting actions such as NO facilitated vasodilation

Saltiki, K and Alevizaki M.. *Hormones*. 2007; 6(1): 9-24

42

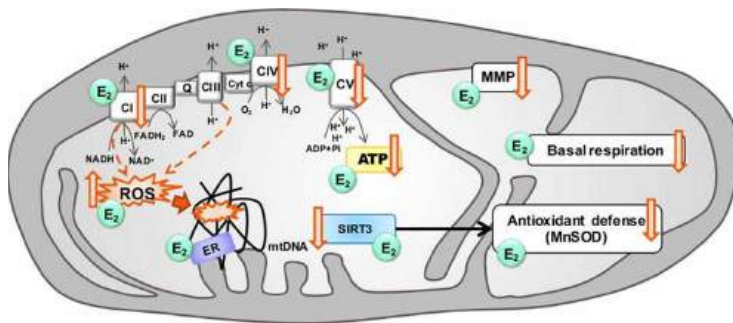


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Modulation of Mitochondrial Function in Aging by Estradiol



↓: age-related decrease, ↑: age-related increase

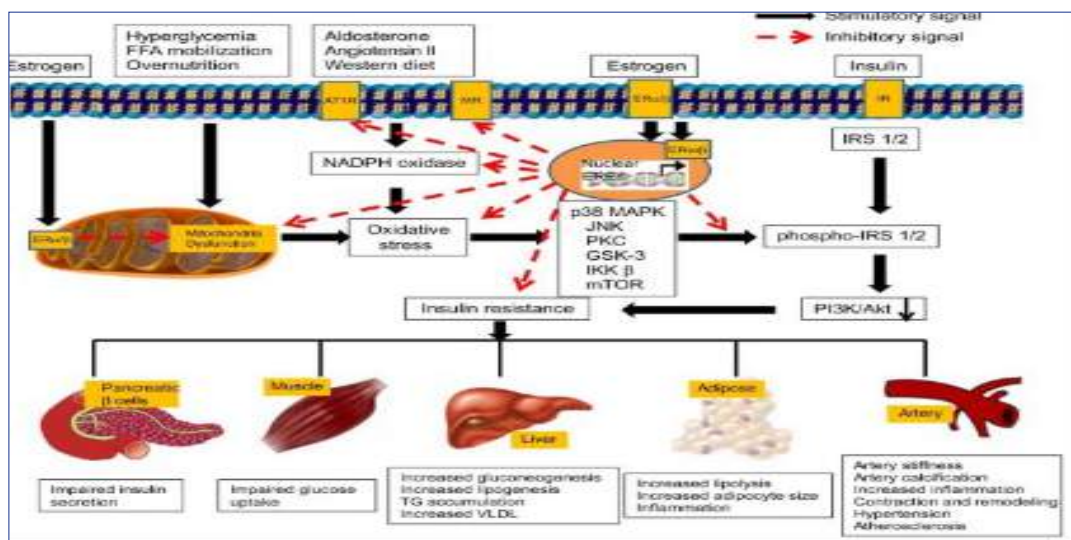
Aging associated with electron transport chain (ETC) impairments:

- Decreased ATP levels, basal respiration & mitochondrial membrane potential (MMP)
- Decreased antioxidant defenses
- Increased ROS production by complex I & complex III
- Increased mitochondrial DNA (mtDNA) oxidative damage
- E2 increases ETC activity, stabilizes MMP, prevents ROS production, ameliorates basal respiration & production of ATP levels
- Sirtuin 3 (SIRT3) + E2 - common pathway to rescue mitochondrial activity in aging by increasing antioxidant defense activity
- E2 & SIRT3 rescue age-related impairments

<https://www.frontiersin.org/articles/10.3389/fnagi.2018.00124/full>
Front. Aging Neurosci., Sec. Cellular and Molecular Mechanisms of Brain-aging, 2018 Volume 10 - 2018

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Estradiol – Master of Metabolic Homeostasis



Rettberg et al. Front Neuroendocrinol. 2014

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Estradiol

E2 directly interacts with mitochondria – a crucial regulator

Mitochondrial Functions

Energy: TCA and OXPHOS
OCR and ECAR
ROS
Steroid biosynthesis
Apoptosis, UPR^{mt}
Fission and Fusion

ERα mRNA
ERβ miRNAs
GPER1 lncRNAs

estrogens → Synthesis metabolism

E2 enhances cellular energy production (ATP synthesis)

E2 improves efficiency of electron transport chain

E2 promotes mitochondrial biogenesis

E2 reduces oxidative stress (ROS)

E2 maintains mitochondrial structure and dynamics (fusion/fission)

ERα ERβ
Src PI3K/Akt MAPK
Rapid signaling NO
Genomic signaling
Nucleus
Inhibition of apoptosis (reduction of autophagy)

Klinge CM. Estrogenic control of mitochondrial function. Redox Biol. 2020 Apr;31:101435. <https://www.frontiersin.org/articles/10.3389/fnagi.2018.00124/full>

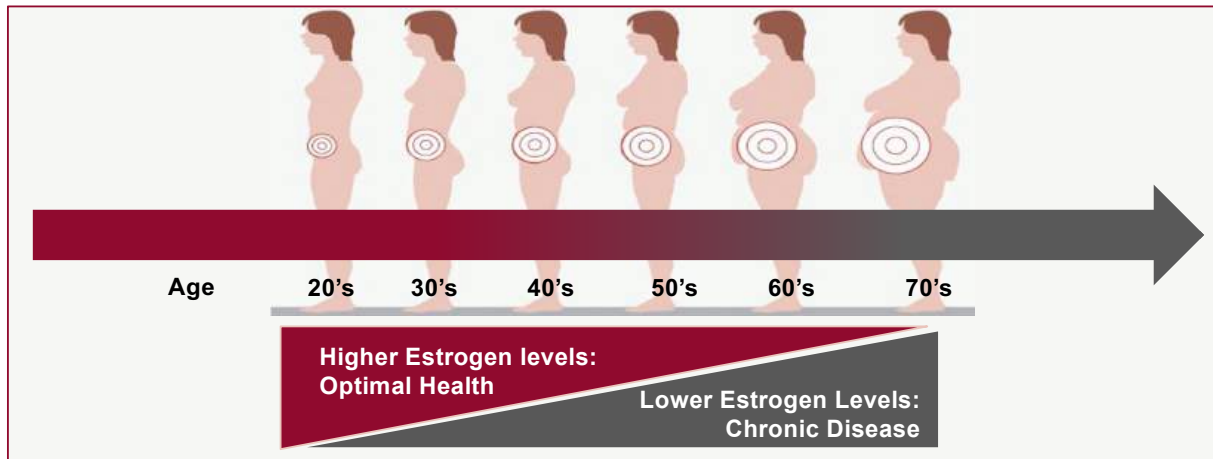
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	Estrogen action	Estrogen deficiency/resistance
	→ Energy balance	→ Obesity
	→ Adipose health	→ Obesity → Adipose inflammation → Altered secretory profile
	→ β-cell function → Survival	→ β-cell dysfunction → Type 2 diabetes
	→ Insulin sensitivity → Lipid homeostasis	→ Insulin resistance → Fatty liver
	→ Insulin sensitivity → Energy homeostasis	→ Insulin resistance → Impaired glucose homeostasis
	→ Macrophage polarization	→ Inflammation → Adiposity → Atherosclerosis

Detrimental Effects of Estradiol Deficiency on Metabolism

Endocr Rev. The role of estrogens in control of energy balance and glucose homeostasis.2013; 34 (3): 309-338

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Adipose tissue inflammation is considered a major contributing factor in the development of obesity-associated insulin resistance and cardiovascular diseases. However, the cause of adipose tissue inflammation is presently unclear. The role of mitochondria in white adipocytes has long been neglected because of their low abundance. However, recent evidence suggests that mitochondria are essential for maintaining metabolic homeostasis in white adipocytes. In a series of recent studies, we found that mitochondrial function in white adipocytes is essential to the synthesis of adiponectin, which is the most abundant adipokine synthesized from adipocytes, with many favorable effects on metabolism, including improvement of insulin sensitivity and reduction of atherosclerotic processes and systemic inflammation. From these results, we propose a new hypothesis that mitochondrial dysfunction in adipocytes is a primary cause of adipose tissue inflammation and compared this hypothesis with a prevailing concept that "adipose tissue hypoxia" may underlie adipose tissue dysfunction in obesity. Recent studies have emphasized the role of the mitochondrial quality control mechanism in maintaining mitochondrial function. Future studies are warranted to test whether an inadequate mitochondrial quality control mechanism is responsible for mitochondrial dysfunction in adipocytes and adipose tissue.

Research Highlight |
Published: 21 August 2020

ADIPOSE TISSUE

ER α affects mitochondrial function in adipocytes

[Claire Greenhill](#) 

Nature Reviews Endocrinology **16**, 625

(2020) | [Cite this article](#)

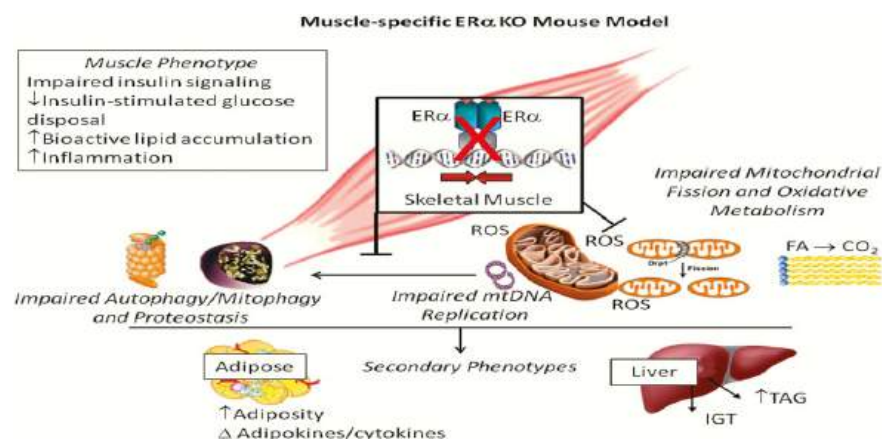
900 Accesses | **3** Citations |
16 Altmetric | [Metrics](#)

- **Estrogen Receptor alpha protects against obesity**
- **Controls metabolism in white & brown adipocytes**
- **Influences mitochondrial remodeling**

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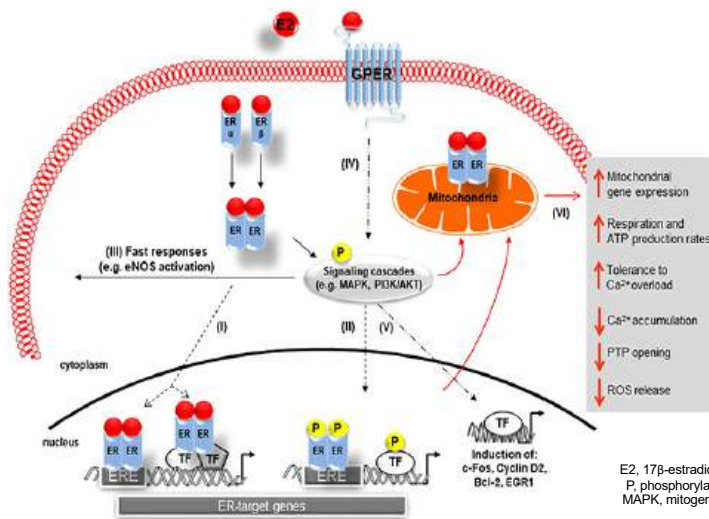
Critical role for ER α in maintenance of muscle mitochondrial & metabolic health

Retention of damaged mitochondria increased ROS production, inflammation, and insulin resistance in skeletal muscle



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E2 induced ER alpha, beta, and G-protein-coupled Estrogen Receptor Signaling: Impacts on Mitochondrial Functioning



E2 initiated cellular & mitochondrial ER/GPER genomic & non-genomic actions modulate mitochondrial respiration, ATP production, & ROS formation

E2, 17β-estradiol; ER, estrogen receptor alpha and beta; ERE, estrogen response element; TF, transcription factor; P, phosphorylation; GPER, G-protein-coupled estrogen receptor; Ca²⁺, calcium; PTP, permeability transition pore; MAPK, mitogen-activated protein kinases; PI3K/AKT, phosphoinositide 3-kinase-serine/threonine-specific kinase B; eNOS, endothelial nitric oxide synthase

Front. Endocrinol., 14 May 2019
Sec. Molecular and Structural Endocrinology
Volume 10 - 2019

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Progesterone Also Enhances Mitochondrial Function



► J Endocr Soc. 2019 Jan 3;3(2):446–467. doi:
[10.1210/js.2018-00219](https://doi.org/10.1210/js.2018-00219)

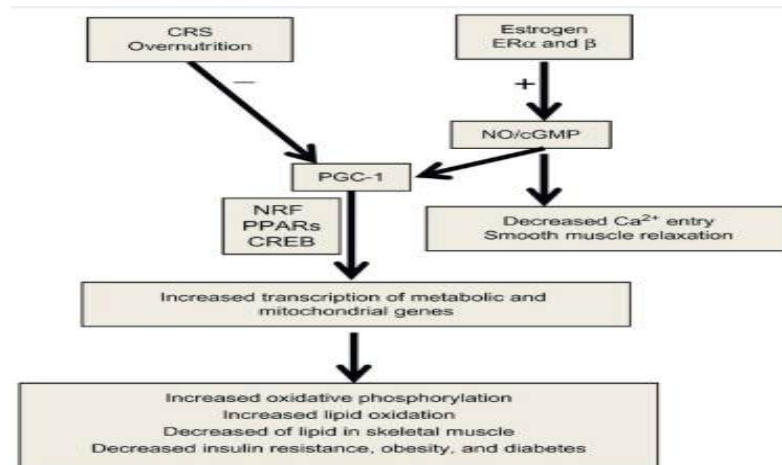
A Mitochondrial Progesterone Receptor Increases Cardiac Beta-Oxidation and Remodeling

Qunsheng Dai¹, Creighton E Likes III¹, Anthony L Luz², Lan Mao³, Jason S Yeh¹, Zhengzheng Wei⁴, Maragatha Kuchibhatla⁵, Olga R Ilkayeva⁶, Timothy R Koves^{6,7}, Thomas M Price¹

- Boosts:
Cellular respiration
Energy (ATP) production
Membrane potential
- Offers protection against oxidative stress and cell death (apoptosis) - brain and reproductive tissues
- Nuclear receptor-dependent and independent mechanisms + specific mitochondrial progesterone receptors (PR-M) identified in humans and primates for energy regulation

54

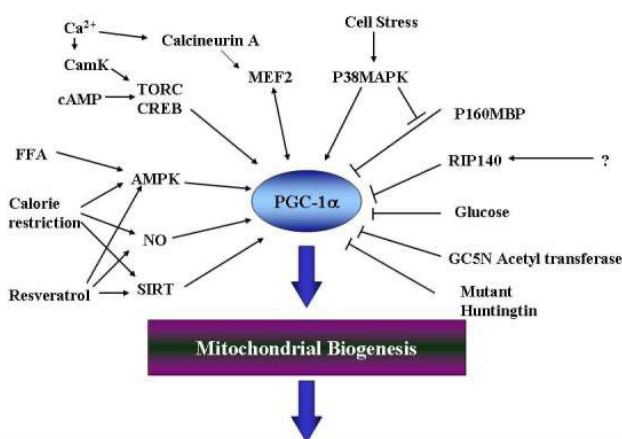
Estradiol and Mitochondrial Function



Rettberg et al. Front Neuroendocrinol. 2014; 35(1):8-30

55

PGC-1 α Activity & Mitochondrial Biogenesis



PGC-1 α – at center of complex network of signals affected by metabolic, nutritional and environmental factors that modulate (through transcriptional and post-translational modifications)

PGC-1 α activity:
Mitochondrial Biogenesis and More

López-Lluch G, Irueta PM, Navas P, de Cabo R. Mitochondrial biogenesis and healthy aging. Exp Gerontol. 2008 Sep;43(9):813-9.

56

The Function and PGC-1 α

PGC-1 α Activity & Mitochondrial Biogenesis

The diagram illustrates the function and activity of PGC-1 α in three tissues: Liver, Brown adipose tissue, and Striated muscle.

- Liver:** Glucocorticoids and cAMP activate FOXO1, which then activates PGC-1 α . Saturated fatty acids activate SREBP, which then activates PGC-1 β . PGC-1 α and PGC-1 β both activate HNF-4, which then activates PPARs and RXRs. PPARs and RXRs lead to Fatty acid oxidation and Gluconeogenesis. PGC-1 α also leads to TAG synthesis and export.
- Brown adipose tissue:** The β_3 -adrenergic/cAMP pathway activates PGC-1 α . PGC-1 α activates NRF-1 and NRF-2, which lead to mtDNA replication, Electron transport, and OXPHOS. PGC-1 α also activates PPARs and RXRs, which lead to Thermogenesis.
- Striated muscle:** p38 MAPK, Calcineurin A/CaMKII, and AMPK activate PGC-1 α . PGC-1 α activates NRF-1 and NRF-2, which lead to mtDNA replication, Electron transport, and OXPHOS. PGC-1 α also activates ER α , which leads to Glucose oxidation. PGC-1 α also activates PPARs and RXRs, which lead to Fatty acid oxidation. PGC-1 α also activates MEF-2, which leads to Glucose uptake.

PGC-1 α (Peroxisome proliferator activated receptor gamma coactivator 1alpha): a transcriptional coactivator – boosts activity of transcription factors that control gene expression

PGC-1 α : master regulator of mitochondrial biogenesis & cellular energy metabolism, promotes oxidative metabolism, & controls how tissues like heart & skeletal muscle use energy & plays crucial role in adaptive thermogenesis

Finck BN, Kelly DP. PGC-1 coactivators: inducible regulators of energy metabolism in health and disease. J Clin Invest. 2006 Mar;116(3):615-22. doi: 10.1172/JCI27794.

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Healthy ovaries - critical for maintaining functional mitochondria

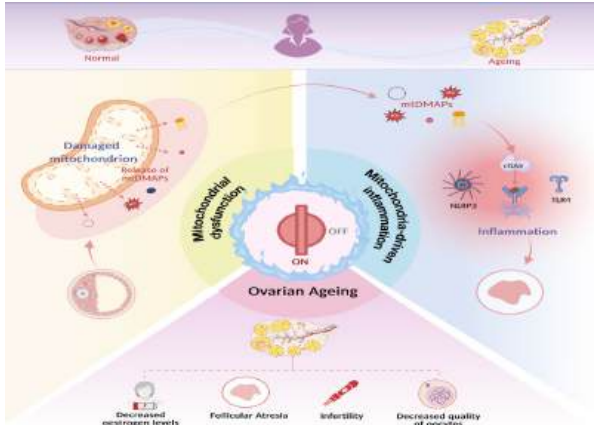
Functional mitochondria - essential for maintaining healthy ovaries: oocyte quality, maturation, embryo development

Ma S et al. Mitochondrial dysfunction in ovarian aging. Chin Med J. 2025;138(23):3069-3082.

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Mitochondrial Inflammation: Triggers Ovarian Aging

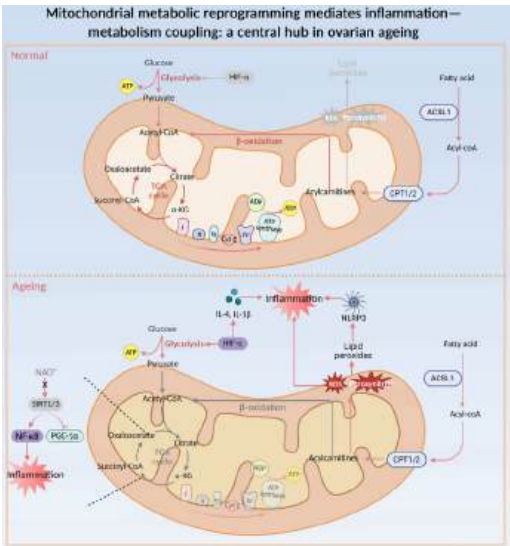
Mechanisms of mitochondria-driven inflammation: Ovarian aging via immune activation



- Mitochondrial dysfunction leads to release of mitochondrial damage-associated molecular patterns (mtDAMPs) - activate innate immune pathways: cGAS, NLRP3, TLR4
- Chronic inflammatory response occurs: local tissue damage & functional decline within ovary + early trigger signal in onset & amplification of ovarian aging

Ju W, Yan B, Li D, Lian F, Xiang S. Mitochondria-driven inflammation: a new frontier in ovarian ageing. J Transl Med. 2025 Sep 24;23(1):1005. doi: 10.1186/s12967-025-06966-6.

Mitochondria - Pivotal Players in Ovarian Aging



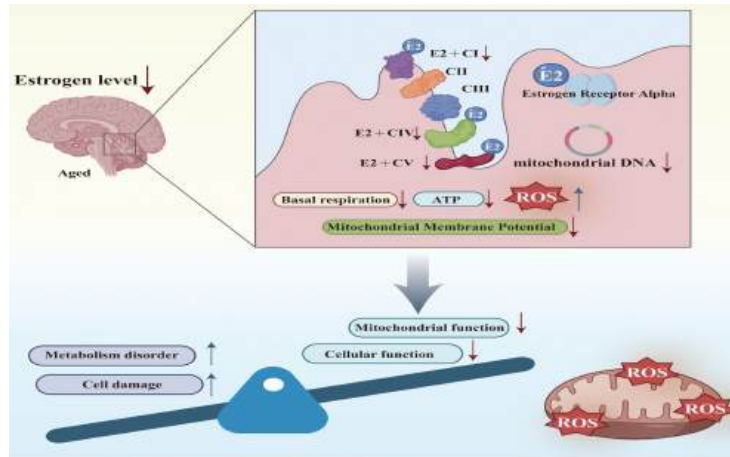
- Mitochondrial metabolism undergoes reprogramming - enhanced glycolysis, reduced efficiency of TCA cycle and fatty acid β -oxidation, accumulation of metabolic intermediates - resulting in impaired energy production
- Lipid peroxidation and metabolic dysregulation further aggravate inflammatory responses, establishing vicious cycle of metabolic— inflammatory feedback -

Mitochondria shift from centers of metabolic homeostasis to pro-inflammatory metabolic hubs & drivers of ovarian functional decline & the acceleration of aging



Ju W, Yan B, Li D, Lian F, Xiang S. Mitochondria-driven inflammation: a new frontier in ovarian ageing. J Transl Med. 2025 Sep 24;23(1):1005. doi: 10.1186/s12967-025-06966-6.

Reduced Estrogen & Mitochondrial Function during Aging:



- Reduced E2 affects mitochondrial respiratory chain complexes - reducing basal respiration, ATP production, and membrane potential - while increasing ROS generation
- Reduced E2 alters estrogen receptor interaction and mtDNA levels, leading to mitochondrial dysfunction, metabolic disorders, and cell damage

Huang, X., Pan, CH., Yin, F. *et al.* The Role of Estrogen in Mitochondrial Disease. *Cell Mol Neurobiol* 45, 68 (2025)

61

Estrogen Related Receptor (ERR) Isoforms: Expressed in Myocardium

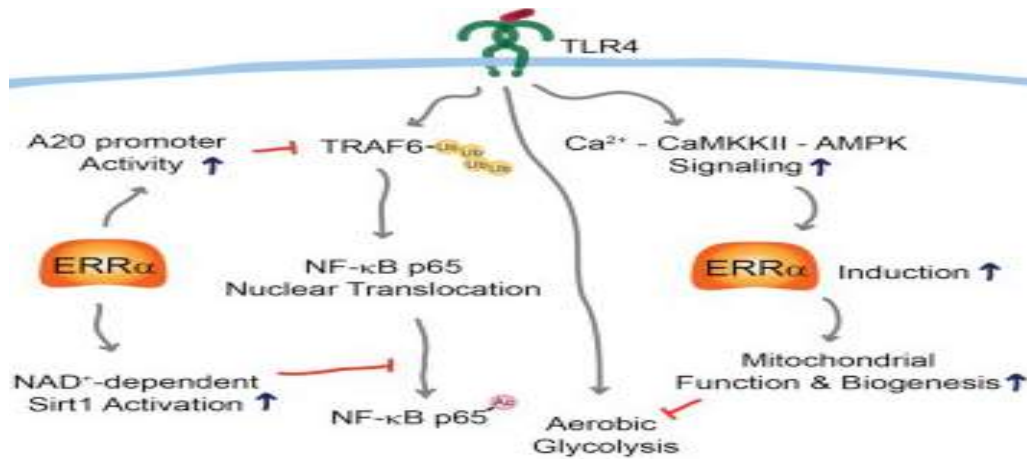
Members of steroid hormone superfamily –
Regulate expression of genes for energy metabolism, mitochondrial biogenesis, fatty acid oxidation, oxidative phosphorylation

ERR α and γ – share target genes in myocardium
ERR β – maintains proper oxygen consumption rates in myocardium

Cunningham et al. Estrogen-Related Receptor α (ERR α) is required for adaptive increases in PGC-1 isoform expression during electrically stimulated contraction of adult cardiomyocytes in sustained hypoxic conditions. *Am J Cardiovasc Dis.* 2016;6(2):46-54

62

E2 Maintains NAD⁺ Levels : Activates SIRT 1 to Reduce Inflammation



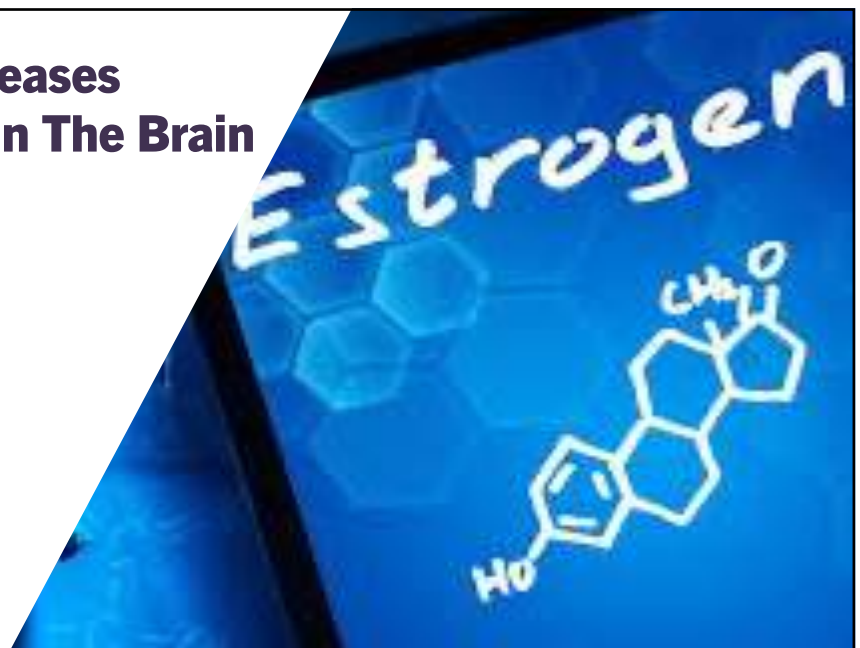
Yuk et al. Immunity. 2015;43(1):80-91

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Estradiol Increases Energy Production in The Brain

E2 increases:

- ATP production
- Mitochondria respiratory rate
- Electron transport

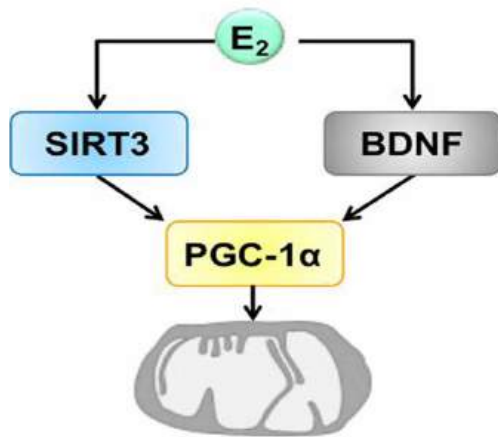


Yao et al. 2012

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E2, BDNF, & SIRT3 + Mitochondria in the Brain

Estrogen (E2) induces expression of BDNF and SIRT3



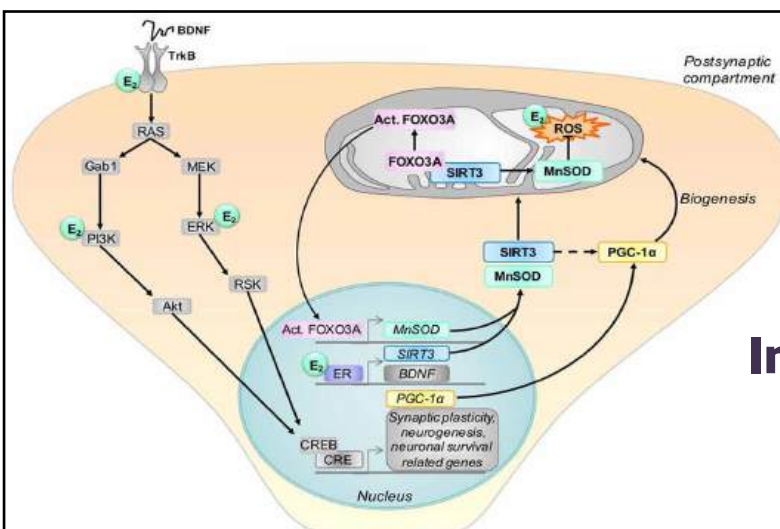
Action of BDNF & SIRT3 converges on mitochondria-regulates expression of PGC-1α
Mitochondrial biogenesis - necessary for synaptic plasticity

E2 enhances mitochondrial quality control - regulates genes associated with mitochondrial autophagy: PINK1 & Parkin - ensure cells maintain normal mitochondrial function in response to stress and injury

BDNF, brain derived neurotrophic factor, PGC-1α, proliferator-activated receptor gamma coactivator 1-alpha, SIRT3, sirtuin 3

<https://www.frontiersin.org/articles/10.3389/fnagi.2018.00124/full>

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Interactions Between Estradiol, BDNF & SIRT3 In Neurons

E2 designates where estradiol may interact with BDNF & SIRT3 pathways

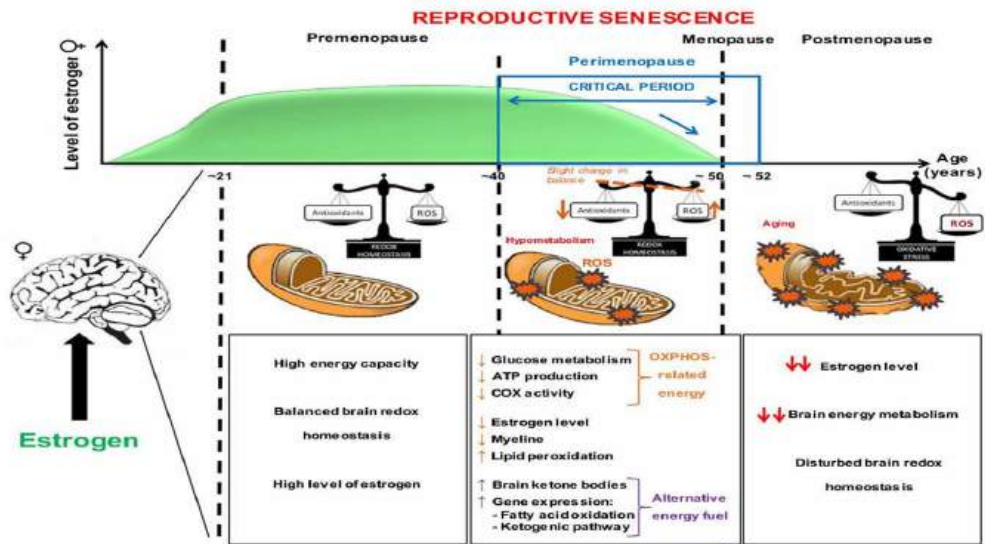
BDNF: brain derived neurotrophic factor, CRE, cAMP response elements, PGC-1α, proliferator-activated receptor gamma coactivator 1-alpha, SIRT3, sirtuin 3

<https://www.frontiersin.org/articles/10.3389/fnagi.2018.00124/full>

Front. Aging Neurosci., Sec. Cellular and Molecular Mechanisms of Brain-aging, 2018 Volume 10 - 2018

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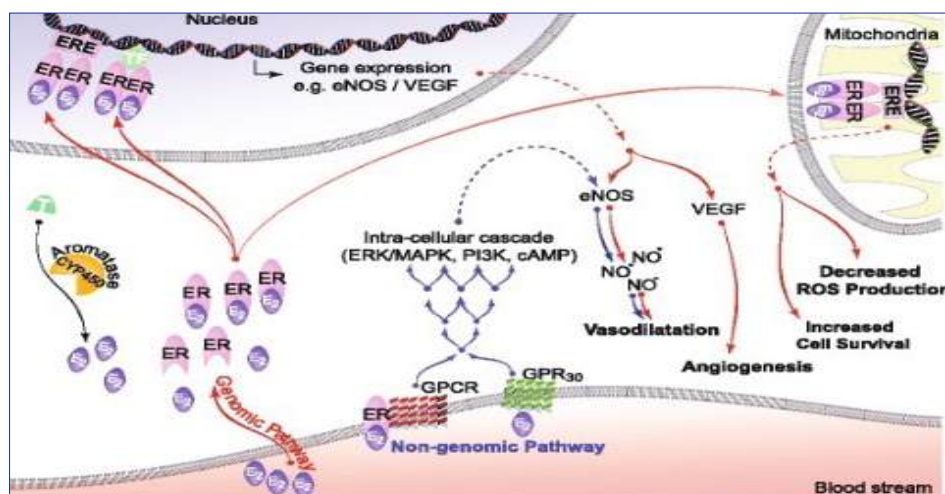
Mitochondria, Estrogen and Female Brain Aging



<https://www.frontiersin.org/articles/10.3389/fnagi.2018.00124/full>

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Normal Conditions: Nitric Oxide & Estradiol: E2 Supports Production of Antioxidant NO



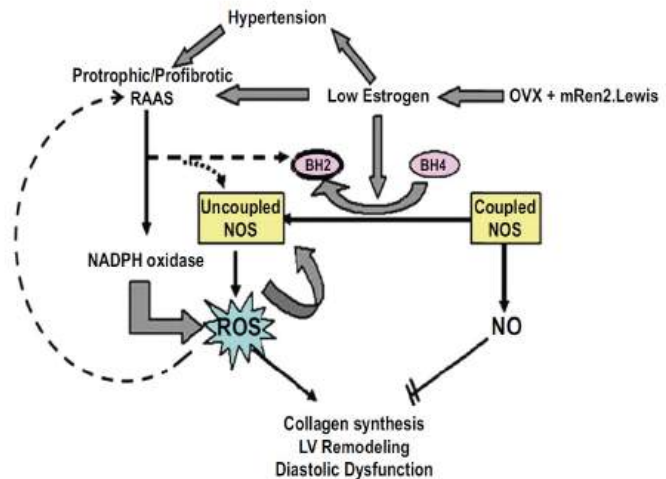
Iorga et al. Biol Sex Differ. 2017; 8: 33.

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Uncoupling of Nitric Oxide

- BH4 - an essential co-factor for all three NOS isoforms
- BH4 regulates NOS at multiple levels
- When BH4 reduced, molecular uncoupling occurs - generation of superoxide (O_2^-) rather than NO

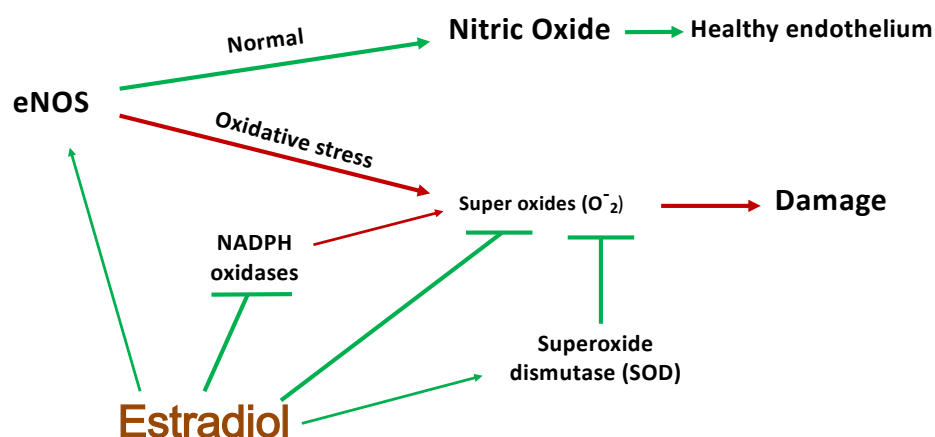
Results in increased ROS & endothelial dysfunction



Moens et al. *Arterioscler Thromb Vasc Biol* 2006;26:2439-44
 Ketonen et al. *Heart Vessels* 2008; 23:420-9
 Zhao Z et al. *Am J Physiol Heart Circ Physiol*. 2013; 306: H628-H640

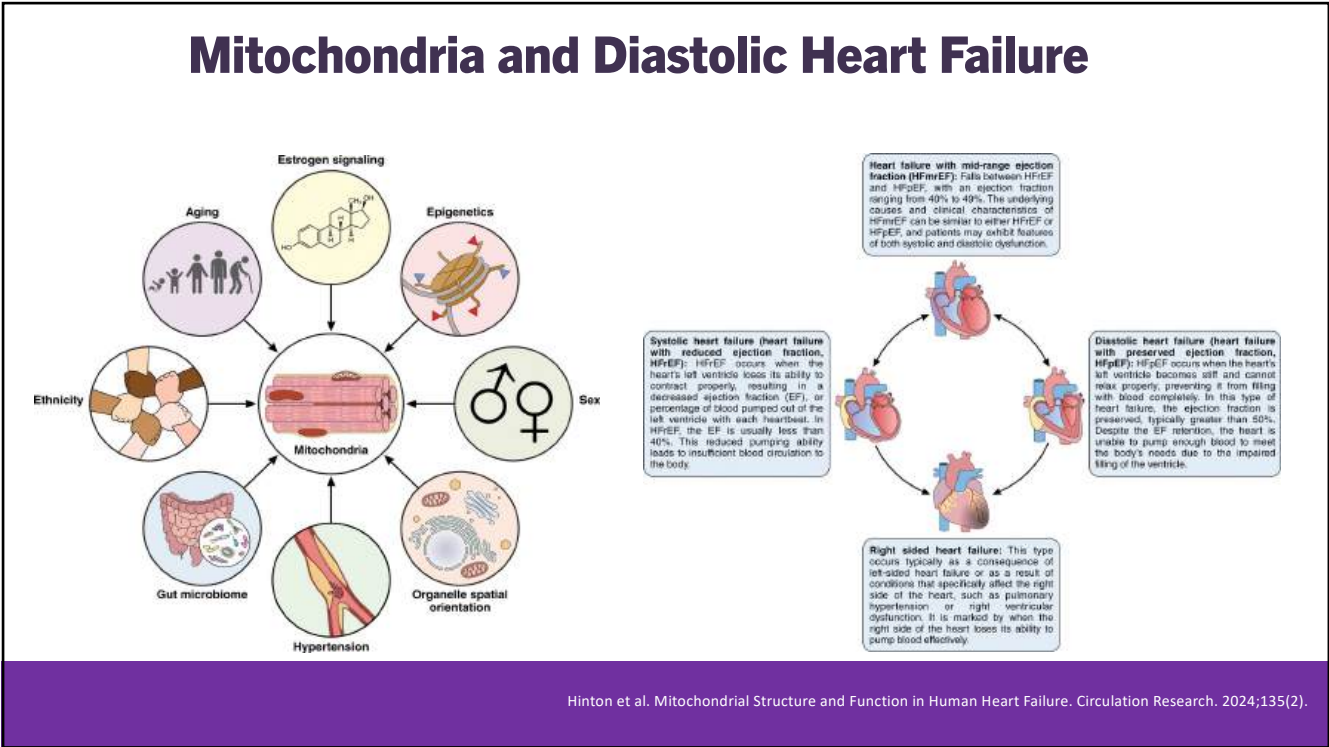
69

Estradiol: Anti-inflammatory Properties to Support Nitric Oxide Production + Function

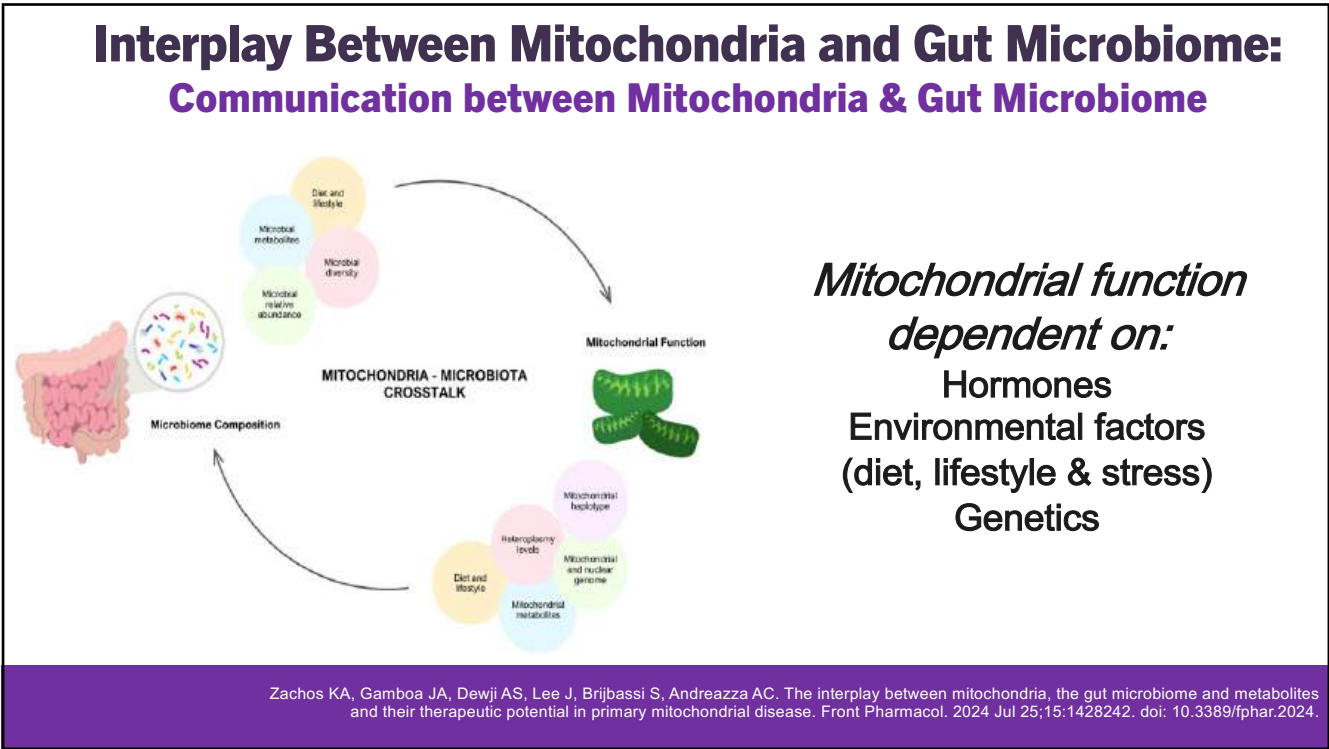


Chakrabarti S, et al. Estrogen is a modulator of vascular inflammation. *IUBMB Life*. June 2008; 60(6): 376-382

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Mitochondria and the Autonomic Nervous System (ANS)

Mitochondria - Essential energy providers for ANS

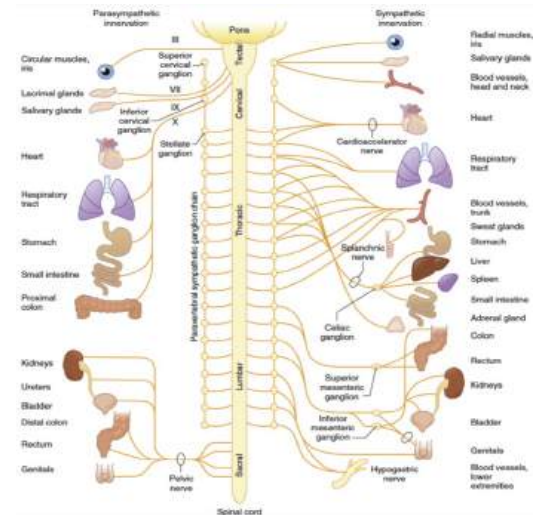
Mitochondrial dysfunction severely impacts ANS regulation –
can lead to orthostatic intolerance,
gastrointestinal issues, reduced stress tolerance

Energy Dependent Regulation

ANS requires high energy to maintain homeostasis

(ie: Digestion, Cardiac Function)

Impairments cause fatigue, dizziness, vertigo, orthostatic intolerance



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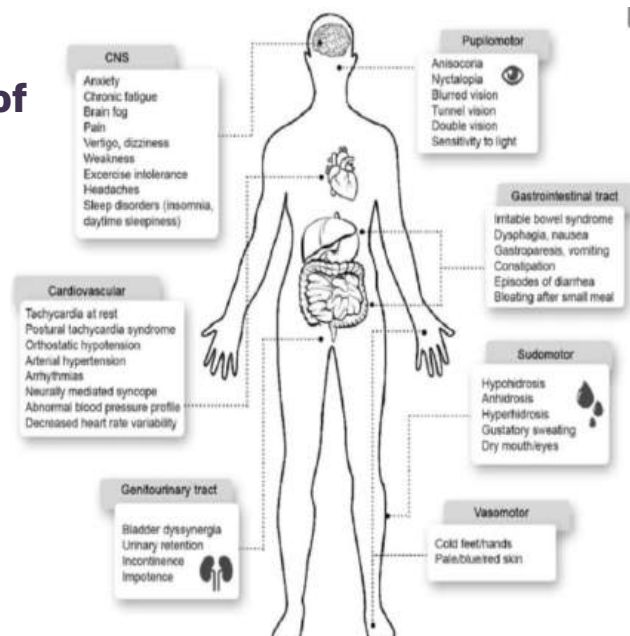
Circadian rhythms are ubiquitous in nature and regulate most, if not all, of our physiological functions, including autonomic activity

Autonomic dysfunction and chronic disease

Nov 2018 · *British Medical Bulletin* 128(1)

DOI: [10.1093/bmb/ldy036](https://doi.org/10.1093/bmb/ldy036)

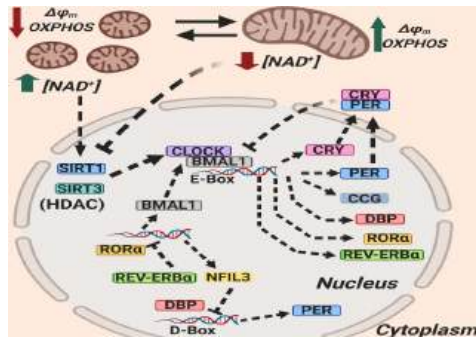
Pawel Zalewski · Joanna Słomko ·
Monika Zawadka-Kunikowska



Chapter 28 - Circadian rhythms and autonomic function Diego A. Golombék, Daniel E. Vigo,
Editor(s): Italo Biaggioni, Kirsteen Browning, Gregory Fink, Jens Jordan, Phillip A. Low, Julian F.R. Paton Primer on the Autonomic Nervous System (Fourth Edition),
Academic Press, 2023, Pages 161-164

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Circadian clock regulates mitochondrial function & metabolic products, specifically NAD⁺ & reactive oxygen species (ROS) - feedback signals to molecular clock



Cite this article as: Shanmugam V, Wall A, Al-Taweel N & Büchelberg B. Disruption of circadian rhythm increases the risk of cancer, metabolic syndrome and cardiovascular disease, *Journal of Local and Global Health Science*, 2013; 5: <http://dx.doi.org/10.5399/jlghs.2013.5>

Bruno A Aguilar-López et al. Front Cell Dev Biol 2020

Optimization: Mitochondrial Function & Metabolic Health

1. FEED THE GUT + TARGETED SUPPLEMENTS
2. EAT TO THE BEAT
3. STEP INTO THE LIGHT
4. GET ADEQUATE AND RESTORATIVE SLEEP
5. EXERCISE ANY TIME POSSIBLE
6. LIVE CLEAN AND PURE

7. PERSONALIZE THE PLAN



Sodium Butyrate - Key Regulator of Mitochondrial Function

Sodium Butyrate as Key Regulator of Mitochondrial Function and Barrier Integrity of Human Glomerular Endothelial Cells

Maria Novella Nicese et al. Int J Mol Sci. 2023.

Poultry Science
Volume 104, Issue 9, September 2025, 105476

Full-Length Article
Sodium butyrate attenuates lipid metabolism disorder via improving mitochondrial function and activating autophagy in LMH cells

Sasa Miao ^a, Mengru Xu ^b, Fang Liu ^b, Xinyang Dong ^b, Xiaoting Zou ^b, Tao Zeng ^a, Lizhi Lu ^a 

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Fatty liver, Oxidative Stress, & Mitochondrial Dysfunction
Key Pathophysiological Features of Insulin Resistance & Obesity

Butyrate Regulates Liver Mitochondrial Function, Efficiency, and Dynamics in Insulin-Resistant Obese Mice

Maria Pina Mollica et al. Diabetes. 2017 May.

Butyrate, produced by fermentation in large intestine by gut microbiota + its synthetic derivative, N-(1-carbamoyl-2-phenyl-ethyl) butyramide, FBA, demonstrated protective against insulin resistance & fatty liver

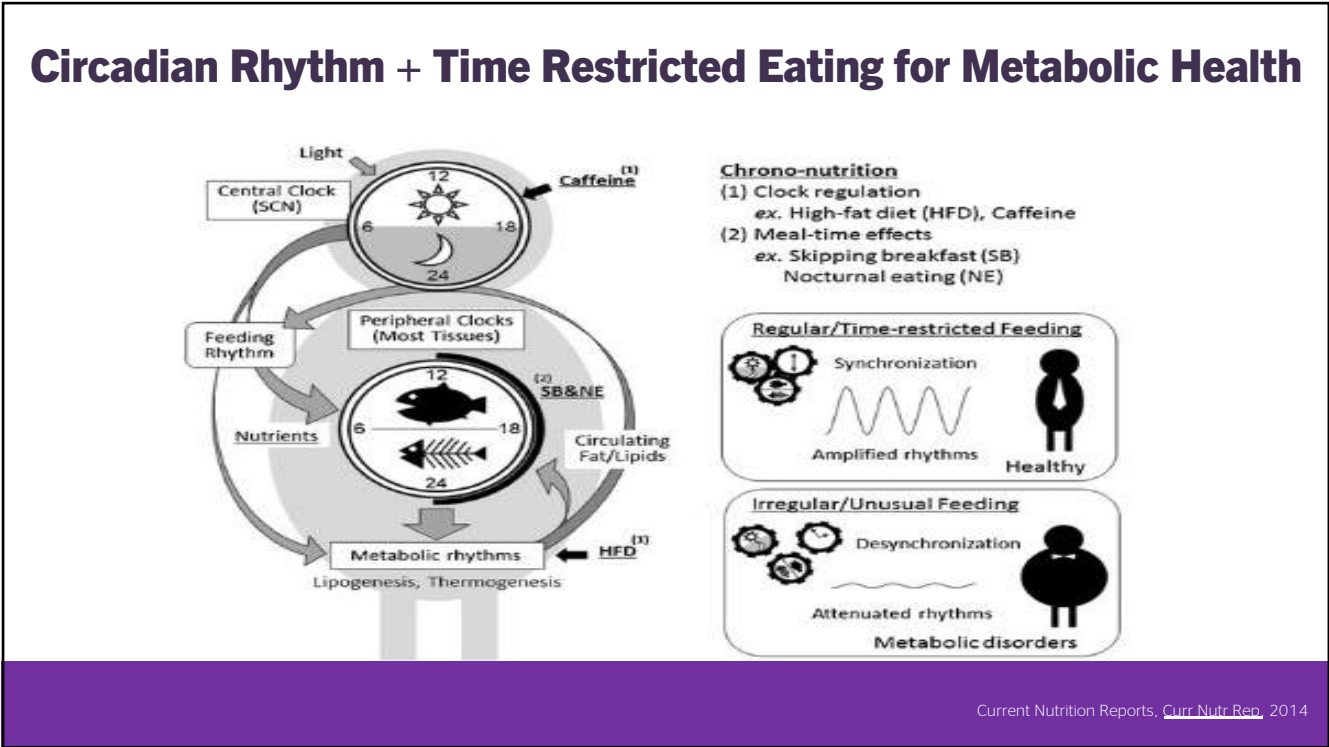
Hepatic mitochondria identified as main target of beneficial effect of butyrate-based compounds in reverting insulin resistance & fat accumulation in diet-induced obese mice

Butyrate & FBA improved respiratory capacity & fatty acid oxidation, activated AMPK-acetyl-CoA carboxylase pathway. Both treatments increased utilization of substrates, especially fatty acids, leading to reduction of intracellular lipid accumulation & oxidative stress

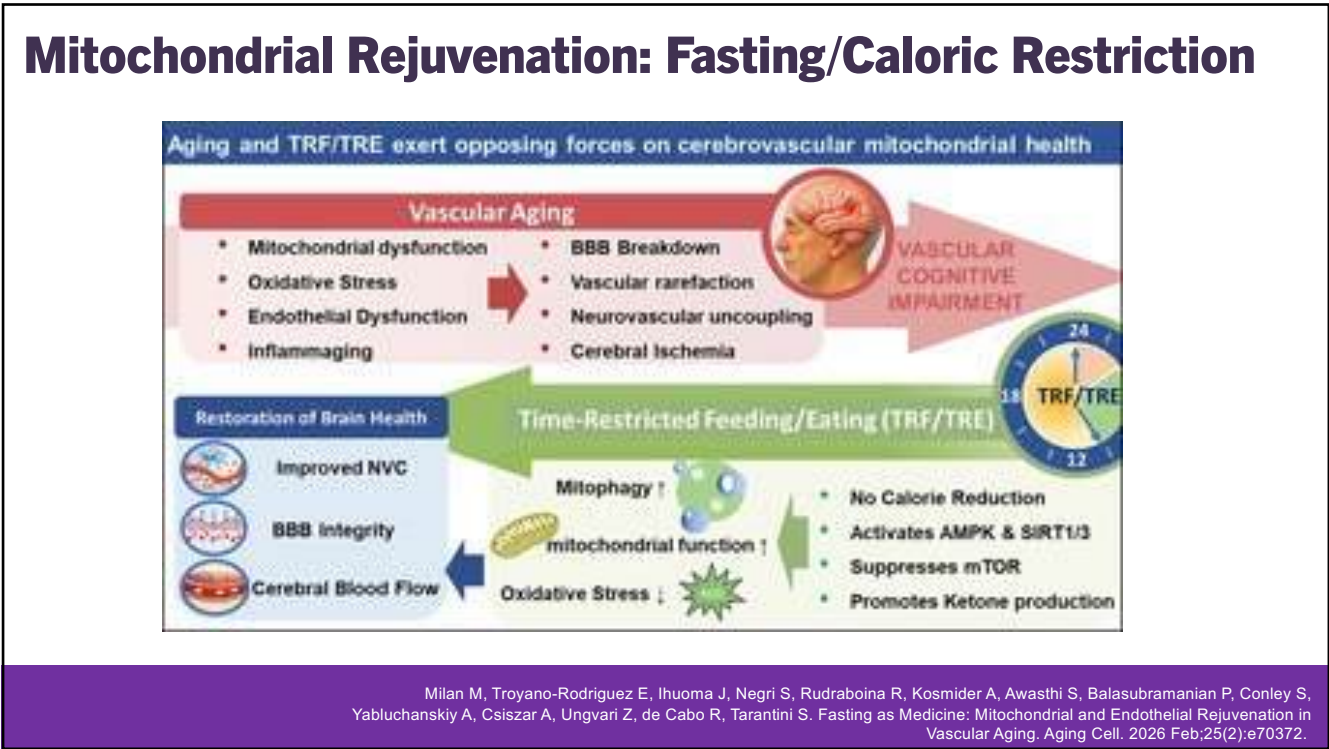
Shift of mitochondrial dynamic toward fusion by butyrate & FBA resulted in improvement of mitochondrial cell energy metabolism & glucose homeostasis

*Butyrate modulates mitochondrial function, efficiency, and dynamics -
New therapeutic strategy to counteract obesity & insulin resistance*

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Mitochondrial Rejuvenation Approaches: Vagus Nerve Stimulation

Published: 26 May 2016

Vagus Nerve Stimulation Exerts the Neuroprotective Effects in Obese-Insulin Resistant Rats, Leading to the Improvement of Cognitive Function

These findings suggest that VNS attenuates cognitive decline in obese-insulin resistant rats by attenuating brain mitochondrial dysfunction, improving brain insulin sensitivity, decreasing cell apoptosis and increasing dendritic spine density.

Chen, T., Samson, R., Sripetchwong, J. et al. Vagus Nerve Stimulation Exerts the Neuroprotective Effects in Obese-Insulin Resistant Rats, Leading to the Improvement of Cognitive Function. *Sci Rep* 6, 26886 (2016). <https://doi.org/10.1038/srep26886>

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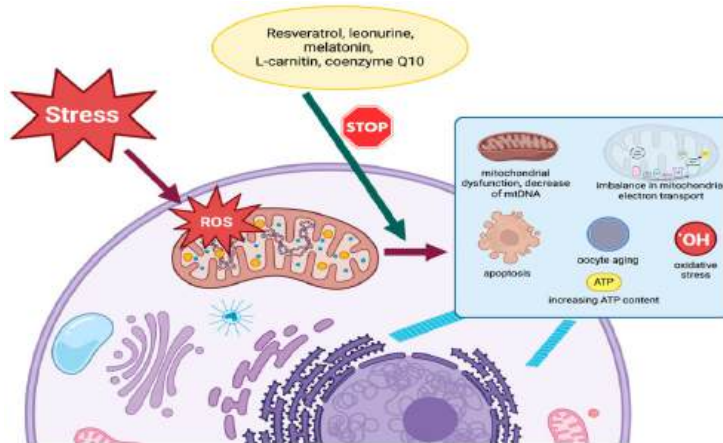
Mitochondrial Rejuvenation Approaches: Vagus Nerve Stimulation

Vagus Nerve Stimulator
Laughter yoga
Guided meditation & biofeedback - heartrate variability
Meditation
Breathwork
Singing and chanting
Gargling

Cold plunges
Acupuncture
Massage
Essential oils
Gut Microbiome support: Probiotics & Prebiotics
Support Circadian Rhythm
Adrenal adaptogens
Exercise
Socializing

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Beneficial Effects of Different Substances on Mitochondrial Functions



Gałęska E, Kowalczyk A, Wrzecińska M, García MC, Czemińska-Piątkowska E, Gwoździwicz S, Witkiewicz W, Dobrzański Z. The Importance of Mitochondrial Processes in the Maturation and Acquisition of Competences of Oocytes and Embryo Culture. *Int J Mol Sci*. 2025 Apr 25;26(9):4098.

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Therapeutic Approaches Targeting Mitochondria

Supplements to help restore mitochondrial activity:

- Coenzyme Q (Ubiquinol)
- N-acetylcysteine (NAC)
- Alpha-lipoic acid
- NAD⁺ precursors
- Urolithin a
- Vitamin D
- Vitamin C
- Vitamin E
- Vitamin A
- B Vitamins
- Butyrate
- Selenium
- Resveratrol
- Leonurine
- Spermidine
- Melatonin
- L Carnitine
- Probiotics
- Omega 3
- Repair Gut Microbiome Support
- Magnesium

Zhang, J., Bao, Y., Zhou, X. *et al.* Polycystic ovary syndrome and mitochondrial dysfunction. *Reprod Biol Endocrinol* 17, 67 (2019). <https://doi.org/10.1186/s12958-019-0509-4>

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Mitochondria and Melatonin

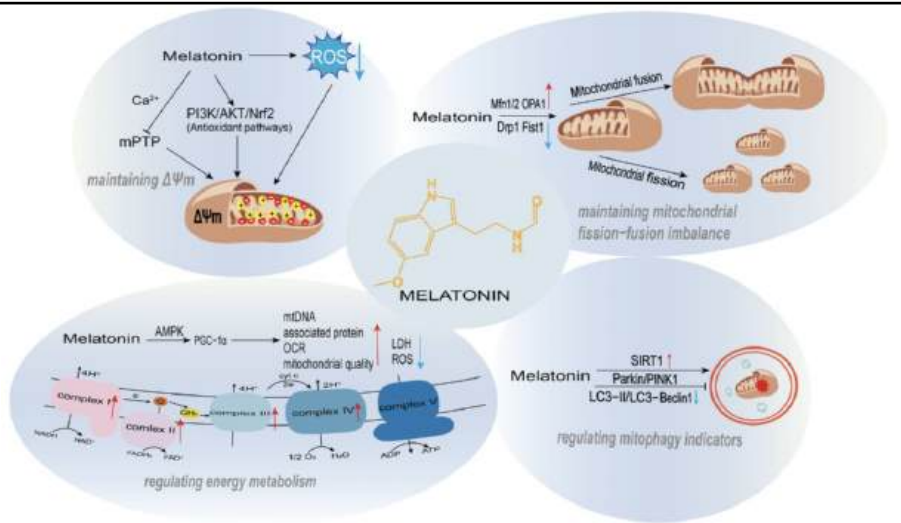


Figure 2. The regulatory roles of melatonin in mitochondrial function. Melatonin supports mitochondrial homeostasis through multiple mechanisms, including the maintenance of mitochondria membrane potential, regulation of mitochondrial quality control, promotion of mitochondrial biogenesis, and modulation of energy metabolism.

Bao Y et al. Melatonin as a Guardian of Mitochondria: Mechanisms and Therapeutic Potential in Neurodegenerative Diseases. *Biology*. 2026; 15:189.

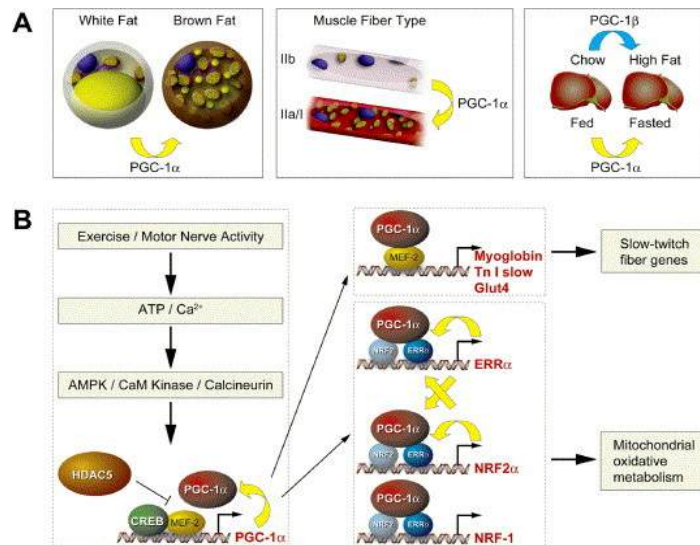
Omega 3 and Mitochondrial Function

Scientific literature from in vitro and in vivo studies - pivotal role of mitochondrial dysfunctions in molecular pathogenesis of multiple diseases: cancer, neurodegenerative diseases, cardiovascular diseases, etc

Oxidative stress - important role in pathogenesis of many diseases & in mitochondrial functions

- *Omega-3 fatty acids improve mitochondria-related redox status.*
- *Omega-3 fatty acids trigger mitochondria-related cell death.*
- *Omega-3 fatty acids modulate mitochondrial biogenesis.*
- *Omega-3 fatty acids restore mitochondria-related bioenergetics*

Marcos Roberto de Oliveira, Seyed Fazel Nabavi, Seyed Mohammad Nabavi, Fernanda Rafaela Jardim, Omega-3 polyunsaturated fatty acids and mitochondria, back to the future, *Trends in Food Science & Technology*, Volume 67, 2017:76-92.



Exercise and Mitochondrial Function

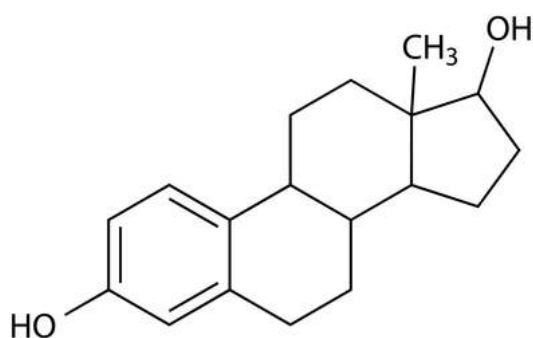
**Exercise
(specifically HIIT)
improves insulin
sensitivity &
mitochondrial
capacity**

Zhang, J., Bao, Y., Zhou, X. *et al.* Polycystic ovary syndrome and mitochondrial dysfunction. *Reprod Biol Endocrinol* **17**, 67 (2019). <https://doi.org/10.1186/s12958-019-0509-4>
<https://www.frontiersin.org/articles/10.3389/fnagi.2018.00124/full>
Front. Aging Neurosci., Sec. Cellular and Molecular Mechanisms of Brain-aging. **2018 Volume 10 - 2018**

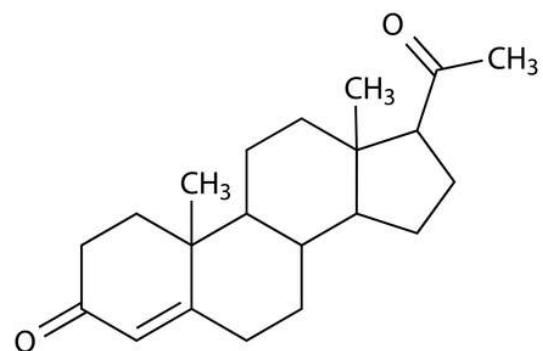
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What About the Use of HRT?

I recommend physiological, cyclic dosing regimens, utilizing human identical hormones (vaginal or rectal P4 administration)



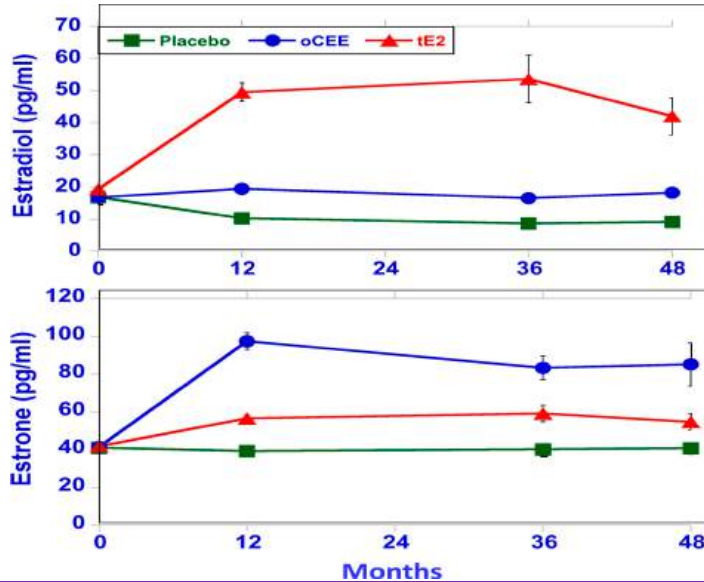
Estradiol



Progesterone

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Low Estradiol Levels and the KEEPS Study



Serum levels of estradiol & estrone in random sample of women (n = 99) participating in Kronos Early Estrogen Prevention Study:

- (oCEE) oral conjugated equine estrogen: 0.45 mg/day
- (tE2) transdermal 17 β -estradiol: 50 μ g/day
- After Women's Health Initiative - recommendations were for use of "lowest" dose of estrogen product.
- Note: serum levels 17 β -estradiol in oCEE-treated group did not exceed levels indicative of menopause required for entry into study

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Neurology®

ARTICLES | August 28, 2001

High-dose estradiol improves cognition for women with AD
Results of a randomized study

DOSE OF ESTRADIOL MATTERS!!

High Serum Estradiol Needed for Optimal Cognitive Health

Asthana S et al. Neurology. 2001;57(4):605-612

90

Bone

Volume 29, Issue 3, September 2001, Pages 216-222

Mechanisms by which high-dose estrogen therapy produces anabolic skeletal effects in postmenopausal women: role of locally produced growth factors

Physiological Levels of Estradiol Needed for Bone Health

Bord S et al. Bone.. 2001; 29(3): 216-222001

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Benefits of Estradiol Replacement Therapy

E2 increases expression of longevity-associated genes, those encoding antioxidant enzymes superoxide dismutase and glutathione peroxidase

- E2 preserves mitochondrial function - can inhibit mitochondrial damage-induced cellular senescence and potentially retard aging process
- E2 prevents senescence in cells, such as endothelial progenitor cells and bone marrow stromal osteoblasts

***17β-E2 prevents depletion of ATP, preserves $\Delta\Psi_m$, and inhibits production of ROS—
and dose matters!***

Lemasters JJ, Qian T, Bradham CA, Brenner DA, Cascio WE, Trost LC, Nishimura Y, Nieminen AL, Herman B. Mitochondrial dysfunction in the pathogenesis of necrotic and apoptotic cell death. J Bioenerg Biomembr. 1999;31:305-319

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Hormone Replacement Therapy in a Nutshell

Estradiol:

- Use topical bioidentical product - commercial patches, gels, compounded cream, not oral or pellets
- Physiological dosing is best - to get a blood level of E2 to 100 pg/ml or higher, as tolerated and per patient’s goals
- Future – possibly vary doses – proliferative (lower) vs secretory (higher) levels

Progesterone:

- Avoid progestins as much as can
- Cyclic P4 for approximately 14 days per month
- Use P4 vaginally (best) or rectally, or topical cream if must, as other options not tolerated
- Dose vaginally or rectally is 200- 400 mg
- Expect controlled, predictable bleeding after finishing the P4

Testosterone:

- Individually evaluated for need and goals
- Stay within the reference range, preferably in the 50 -75th percentile
- Use compounded cream product, not male product or pellets

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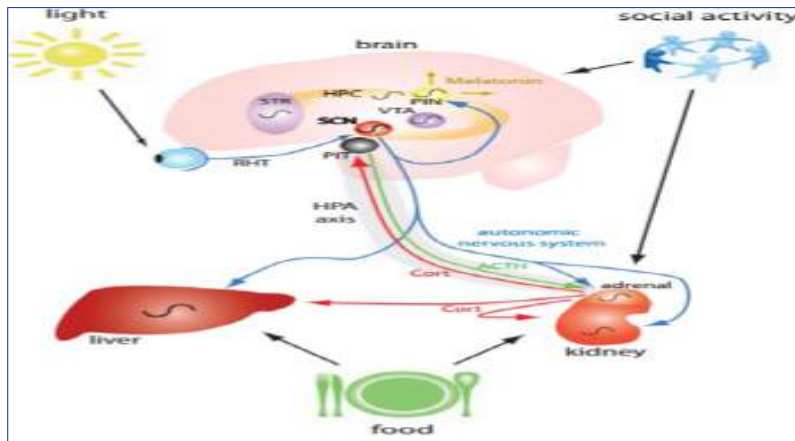
Review				
Table 1 Recommendations for hormone therapy				
Absorption of E2 from any of the commercial products is variable Levels should be monitored at least annually				
Proposed regimen: transdermal E2 patch	Proposed regimen: E2 gel product for use on arm/ thigh	Proposed regimen: micronised oral P4	Conventional regimen: oral E2	Conventional regimen: oral CEE
Apply to abdominal skin twice weekly (every 3-5 days) ► Rotate application site ► Strive for serum E2 level near 100 pg/mL—always above 50 pg/mL ► First month prescribe a 0.05 mg patch ► Check serum E2 level after 1–2 months and increase to 0.075 or 0.1 mg patch, based on E2 level ► Follow serum E2 levels until goal is achieved, then recheck level at least annually. This also applies to gel and patch delivery systems ► Dosing is individualised to patient's goals and symptoms Benefits of transdermal E2: enters blood as E2 and no increased risk of thromboembolism	Month 1: apply one pump to arm each morning ► Check serum E2 level second month and increase to two pumps in AM, one per arm, as indicated by E2 level and symptoms ► Strive for serum E2 level close to 100 pg/mL but always above 50 pg/mL E2 gel product use on thigh ► Month 1: apply contents of pack to anterior thigh each morning ► Start with 1 mg dose ► Check serum E2 level second month and modify dose as indicated by E2 level and symptoms ► Strive for serum E2 level close to 100 pg/mL, always above 50 pg/mL. Dosing is individualised to patient's goals and symptoms	200 mg P4 at bedtime for first 14 days of the month If symptomatic and still having some menses, take P4 at bedtime for the 14 days preceding the expected onset of monthly menstruation Cyclic P4 is recommended for all patients, both with and without a uterus Benefits of cyclic 4 vs static P4: cyclic P4 may lower CVD risk; static P4 may increase it	Regimen 1: take 1–2 mg E2 each morning. Adjust dosage based on symptoms. Regimen 2: take 1 mg E2 twice daily—each morning and evening. Adjust dosage based on symptoms. Why not recommended: conversion to oestrone by liver and increased risk for thromboembolism	Regimen: dose options of CEE are 0.3 mg, 0.45 mg, 0.625 mg or 1.25 mg (most common dose 0.625), adjusting dosage based on symptoms. Why not recommended: conversion of CEE to oestrone and increased risk for thromboembolism Additional commercial product: combination of CEE +bazedoxifene Why not recommended: conversion of CEE to oestrone and lack of human-identical P4, which has recognised health benefits

Transdermal E2+oral micronised P4 for primary CVD prevention and overall quality of life and health.

Gersh FL, et al. Heart 2021;0:1–8. doi:10.1136/heartjnl-2019-316323

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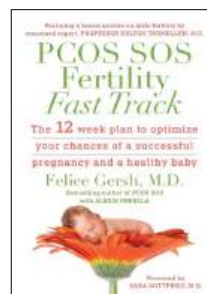
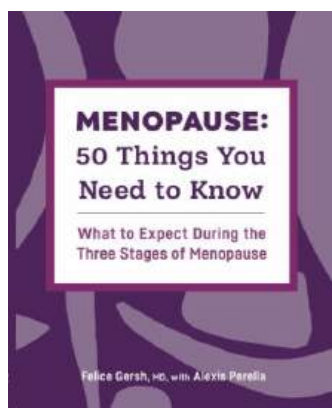
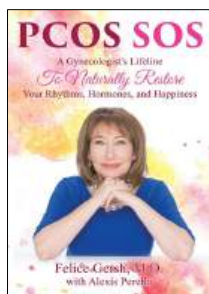
Path to Happy Longevity: Improve HealthSpan by Optimizing E2 & P4 Mitochondrial Function + Lifestyle Medicine



Behav Neurosci 128(3) pg 326-43, 2014.

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Thank you!



Let's keep in touch!

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**NMI
SUMMIT
2026**

**Longevity and Biological Ageing:
Enhancing Health into Advanced Age**

Saturday 10th October

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An event by:  Nutritional Medicine
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