Hormones, the Brain, & the Path to Emotional Balance for Women:

An Integrative Approach

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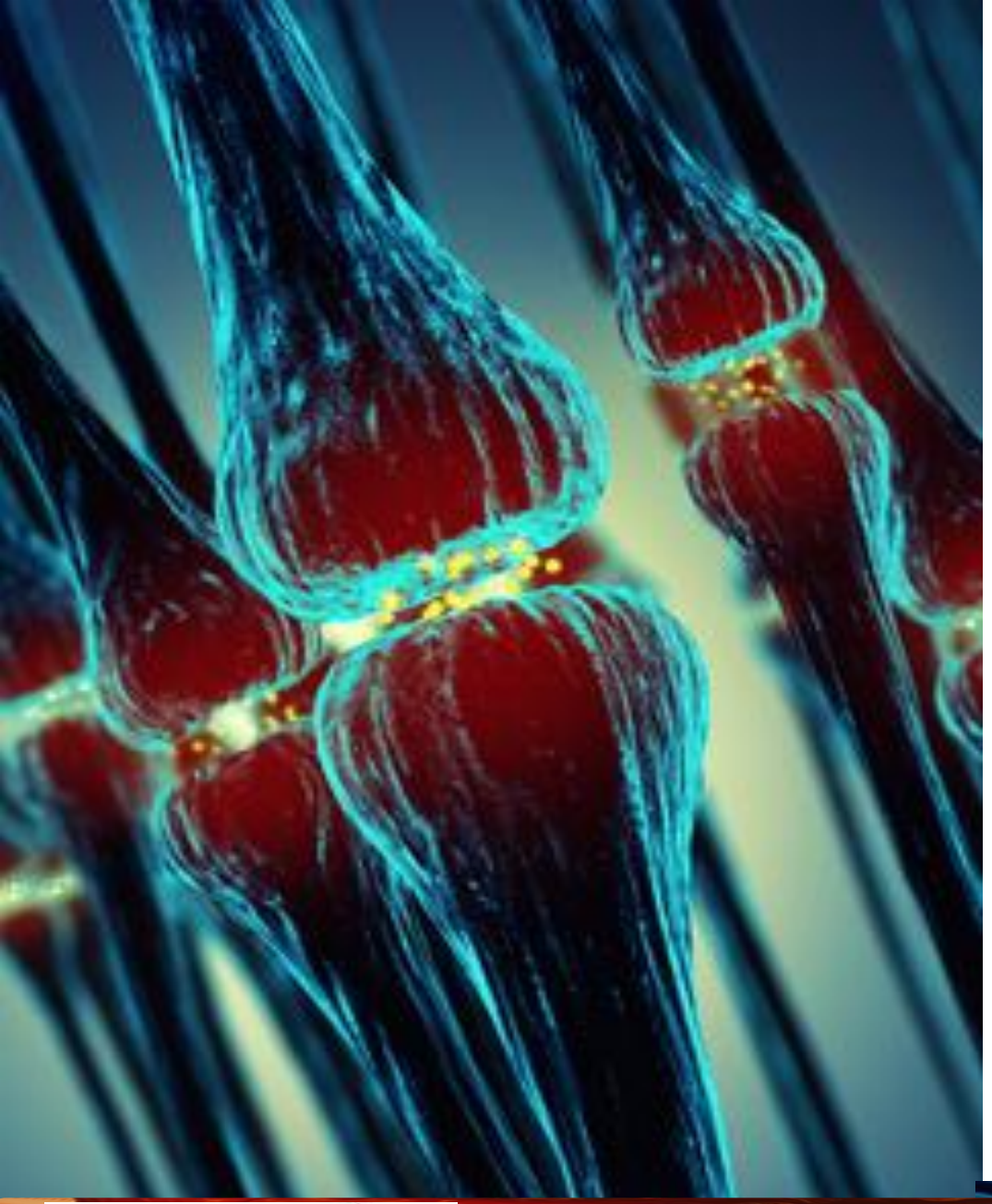
University of Arizona School of Medicine



Learning Objectives

- Review the relationship of ovarian hormones and the brain
- Identify the many ways that sex hormones support brain health and emotional wellbeing
- Design an integrative approach to optimize cognitive and emotional health

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Fundamental of Life:

Optimal Health = Optimal Brain Function

Optimal Hormones

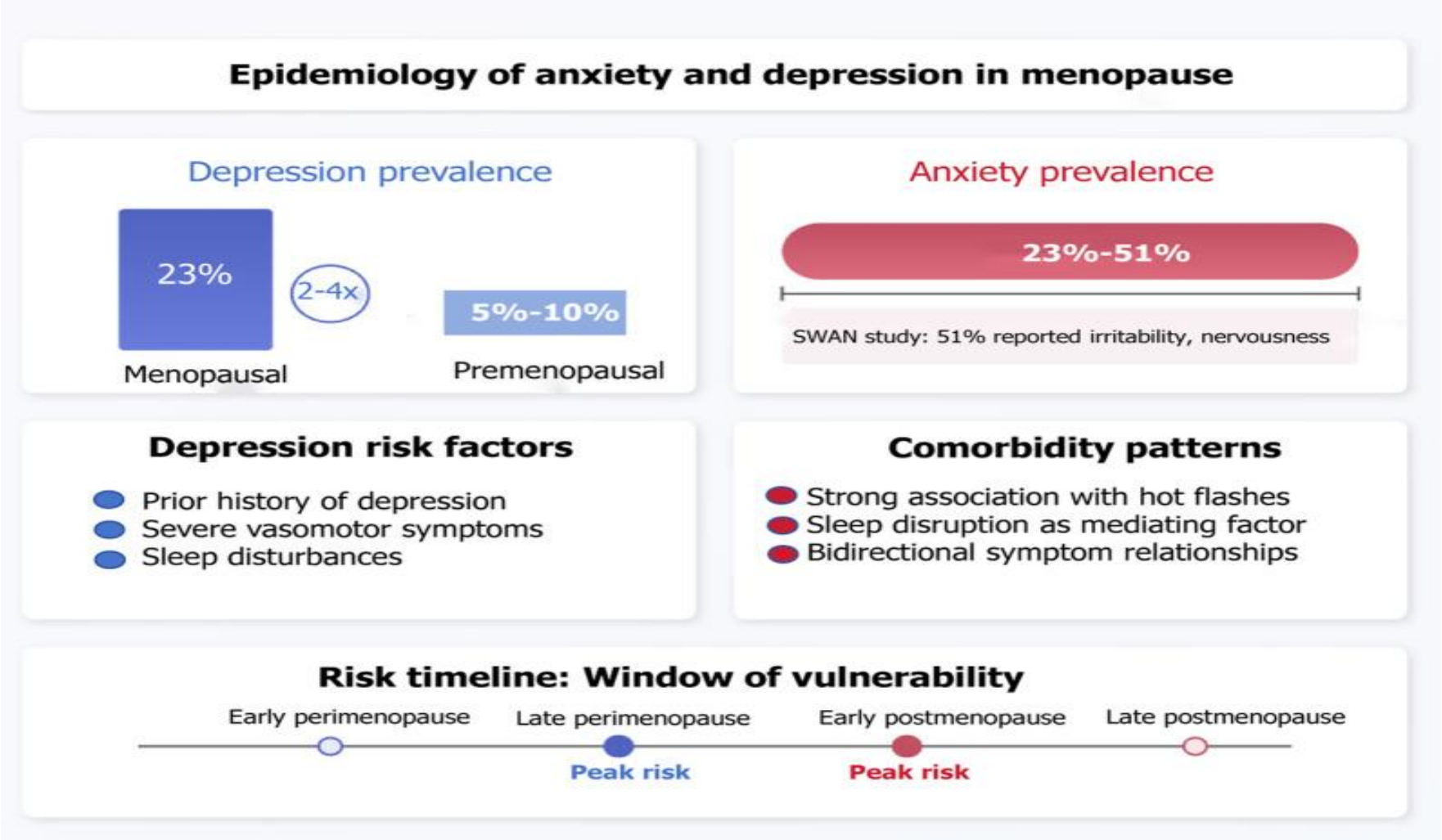
Emotional Impact of Menopause

Fluctuations in estrogen and progesterone levels during menopause affect neurotransmitter systems (including serotonin, norepinephrine, and dopamine), hypothalamic-pituitary-adrenal axis function, inflammatory processes, and neurotrophic factor expression, collectively diminishing the resilience of emotional regulation neural circuits.

Simultaneously, vasomotor symptoms (such as hot flashes and night sweats), sleep disruption, genetic susceptibility, and epigenetic modifications interact with mood disorders, while psychosocial factors (such as midlife stressors and role transitions) and cognitive factors (including negative schemas about aging, attentional bias toward threats, and difficulties in emotional regulation) further shape women's experiences of menopausal changes.

Lang XL, Huang CC, Cui HY, Zhong HX, Shen MY, Zhao F. From physiology to psychology: An integrative review of menopausal syndrome. World J Psychiatry. 2025 Nov 19;15(11):108713.

Prevalence of Menopausal Depression & Anxiety



Lang XL, Huang CC, Cui HY, Zhong HX, Shen MY, Zhao F. From physiology to psychology: An integrative review of menopausal syndrome. World J Psychiatry. 2025 Nov 19;15(11):108713.

Menopause and Melatonin Changes

- **During menopause, women experience a natural, sharp decline in both estrogen and progesterone, which causes a major disruption in melatonin production and overall circadian rhythm**

- **Estrogen withdrawal flattens the body's natural circadian rhythm, resulting in lower melatonin levels, disrupted sleep patterns, and increased anxiety**

- **Decreased endogenous melatonin levels might contribute to the common complaint of sleep disturbances during the menopausal transition and beyond**

Jehan S, Jean-Louis G, Zizi F, Auguste E, Pandi-Perumal SR, Gupta R, Attarian H, McFarlane SI, Hardeland R, Brzezinski A. Sleep, Melatonin, and the Menopausal Transition: What Are the Links? Sleep Sci. 2017 Jan-Mar;10(1):11-18.

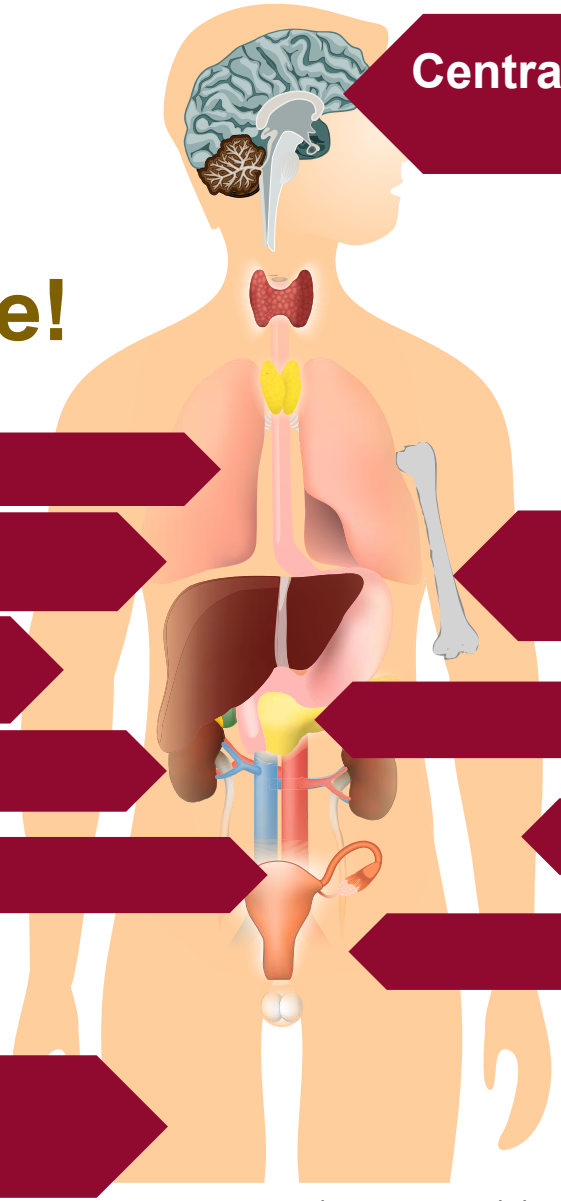
Menopause and Thyroid Function

- Estrogen enhances thyroid function in multiple ways
- If estrogen levels are low - thyroid functioning also goes down
- One main reason why so many women in menopause and perimenopause end up with poor thyroid function
- One in eight women between the ages of 35 and 65 years have some form of thyroid disease
- One in five women over the age of 65 years have some form of thyroid disease

Analyzing Thyroid Dysfunction in the Climacteric Journal of Mid-life Health9(3):113-116, Jul-Sep 2018

Estrogen Receptors:

Located Everywhere!



- Central and Peripheral Nervous system
- Lungs
- Heart
- Endothelium
- Liver
- Bladder
- Mitochondria
- Bone/Joints/Muscle/ Immune Cells
- Gastrointestinal Tract
- Skin
- Ovary/Uterus

Paterni et al. Receptors Alpha and Beta: Subtype Selective Ligands and Clinical Potential, Steroids, 2014; 0:13-29

Estradiol is Neuroprotective

- **Promotes neuronal plasticity - maintains healthy cognitive function + protects against cognitive decline with aging**
- **Increases Brain Derived Neurotrophic Factor (BDNF) & activates its receptor**
- **Promotes neurogenesis in hippocampus to improve learning & memory - Increases dendritic spine number & contacts in hippocampus, amygdala & hypothalamus to support performance on memory tasks**
- **Potentiates synaptic transmission in hippocampus**
- **Essential for optimal neurotransmitter amounts and function**

Kim et al, Neuroscience. 2006
Aguirre et al. EJN 2009; Vol. 29;447-454
Galea et al, J Neuroendocrinol. 2013
Zhao et al, Cell. 2008

Progesterone Receptors:
Widely Dispersed

- Neurological System
- Immune System
- Cardiovascular System
- Skin
- Neurological System
- Musculoskeletal System
- Pancreas

Taraborrelli S. *Acta Obstet Gynecol Scand*. 2015;94:8-16.

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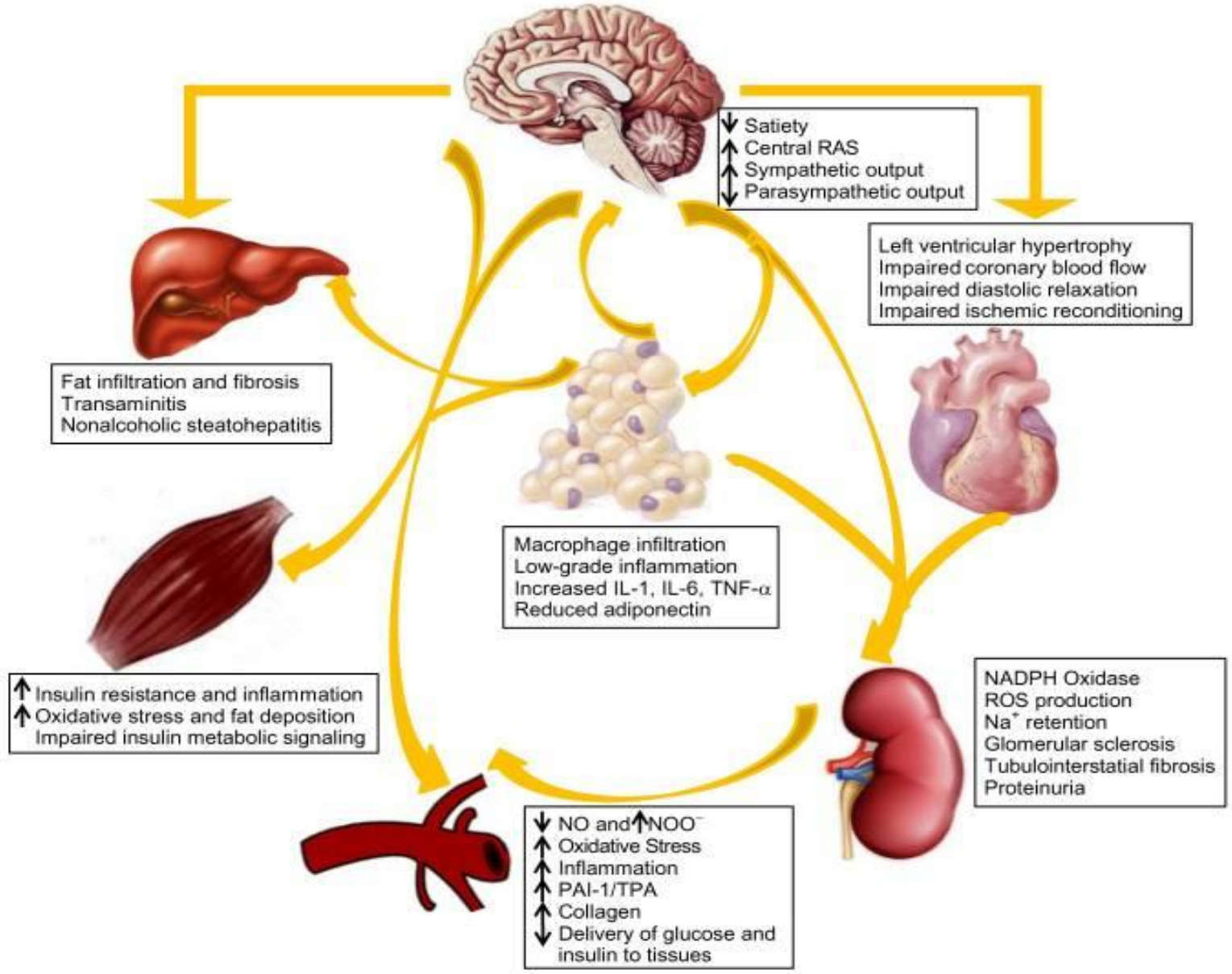
Powerful Progesterone:
Roles in the Brain

- Neurogenesis
- Neuroprotection
- Regulation & Regeneration
- Convulsions
- Myelination
- Traumatic Brain Injury
- Cognition
- Mood Alteration
- Inflammation
- Mitochondrial Function

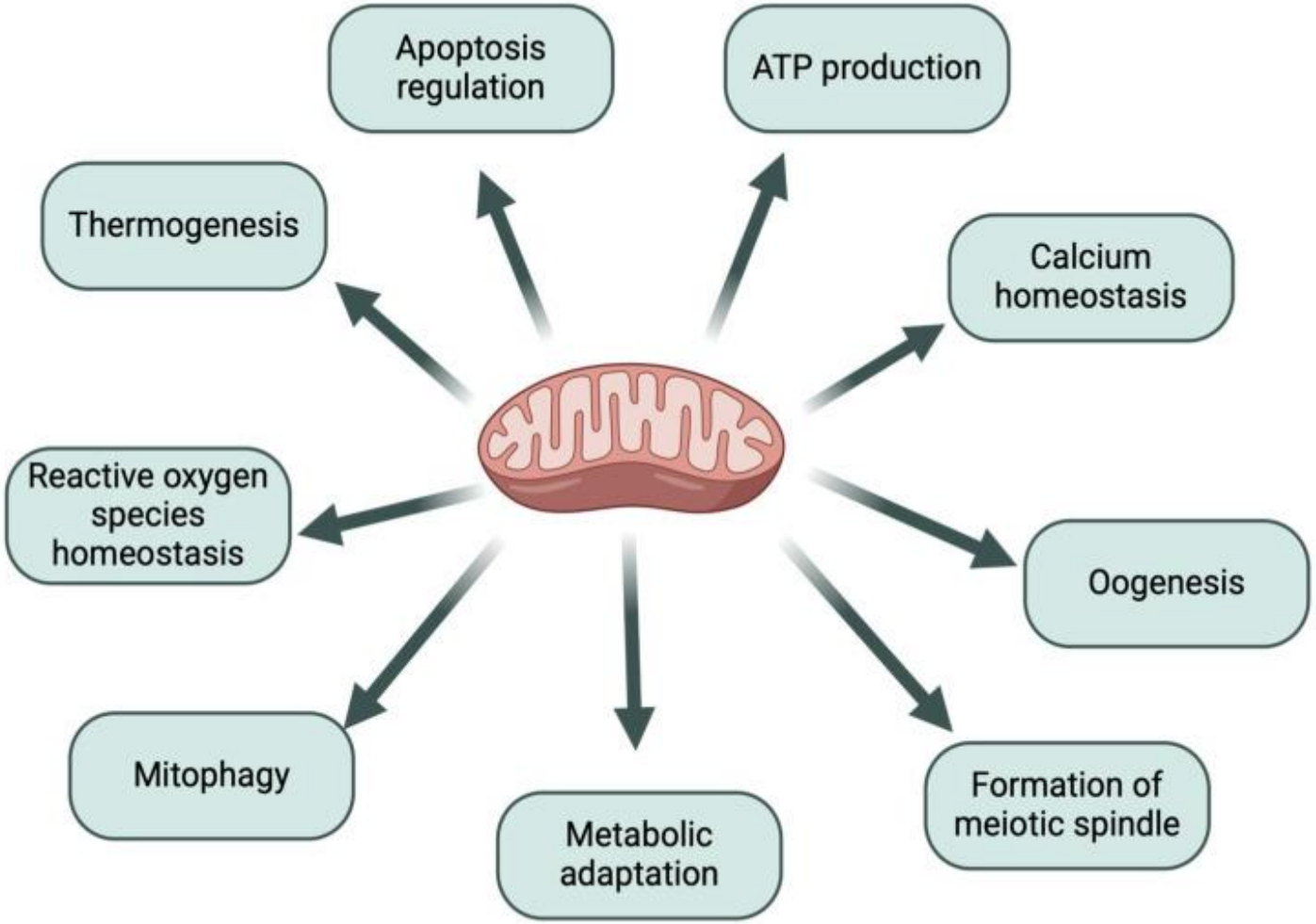
Aggarwal et al; J Pharm Pharmacol 2008;60:731-37

All Systems - Interconnected



Jia G, Aroor AR, Sowers JR. Estrogen and mitochondria function in cardiorenal metabolic syndrome. Prog Mol Biol Transl Sci. 2014;127:229-49.

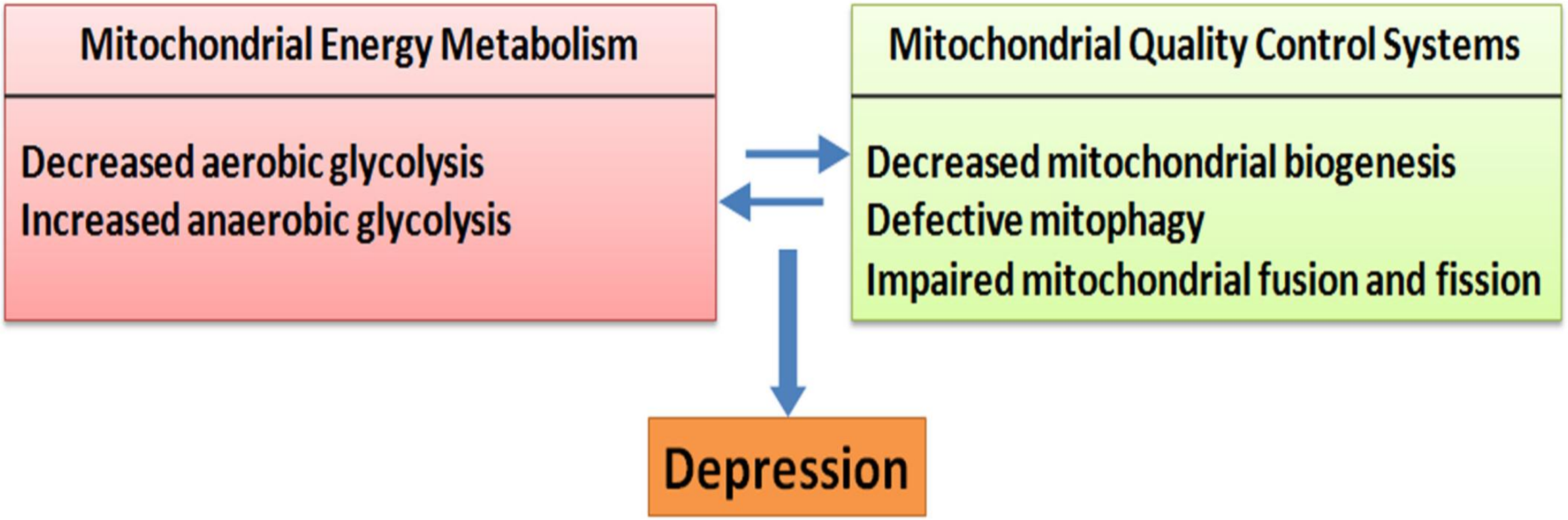
Introducing the Mitochondria



Gałęska E, Kowalczyk A, Wrzecińska M, García MC, Czerniawska-Piątkowska E, Gwoździewicz 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.

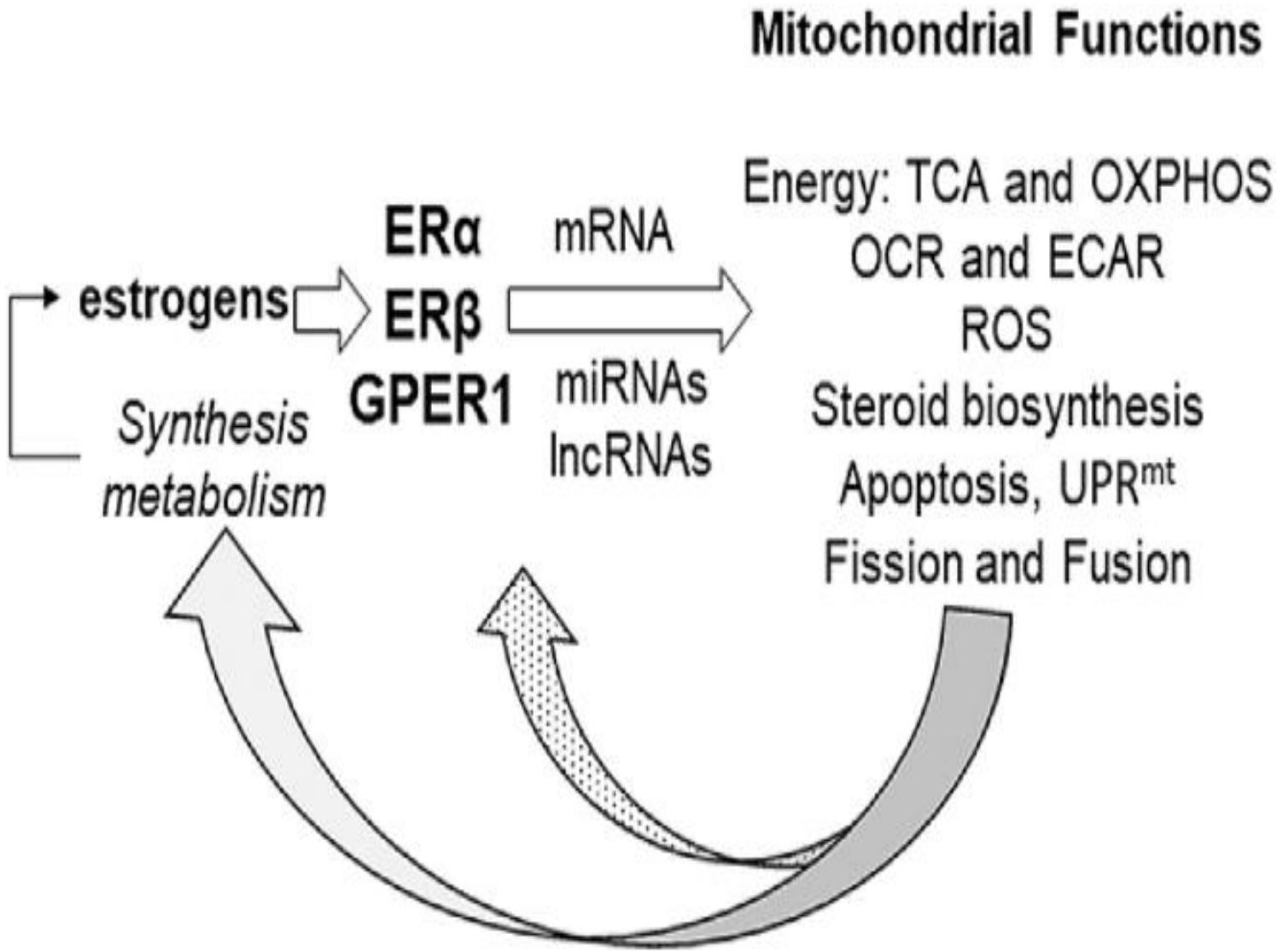
Mitochondria in Depression:

The Dysfunction of Mitochondrial Energy Metabolism and Quality Control Systems



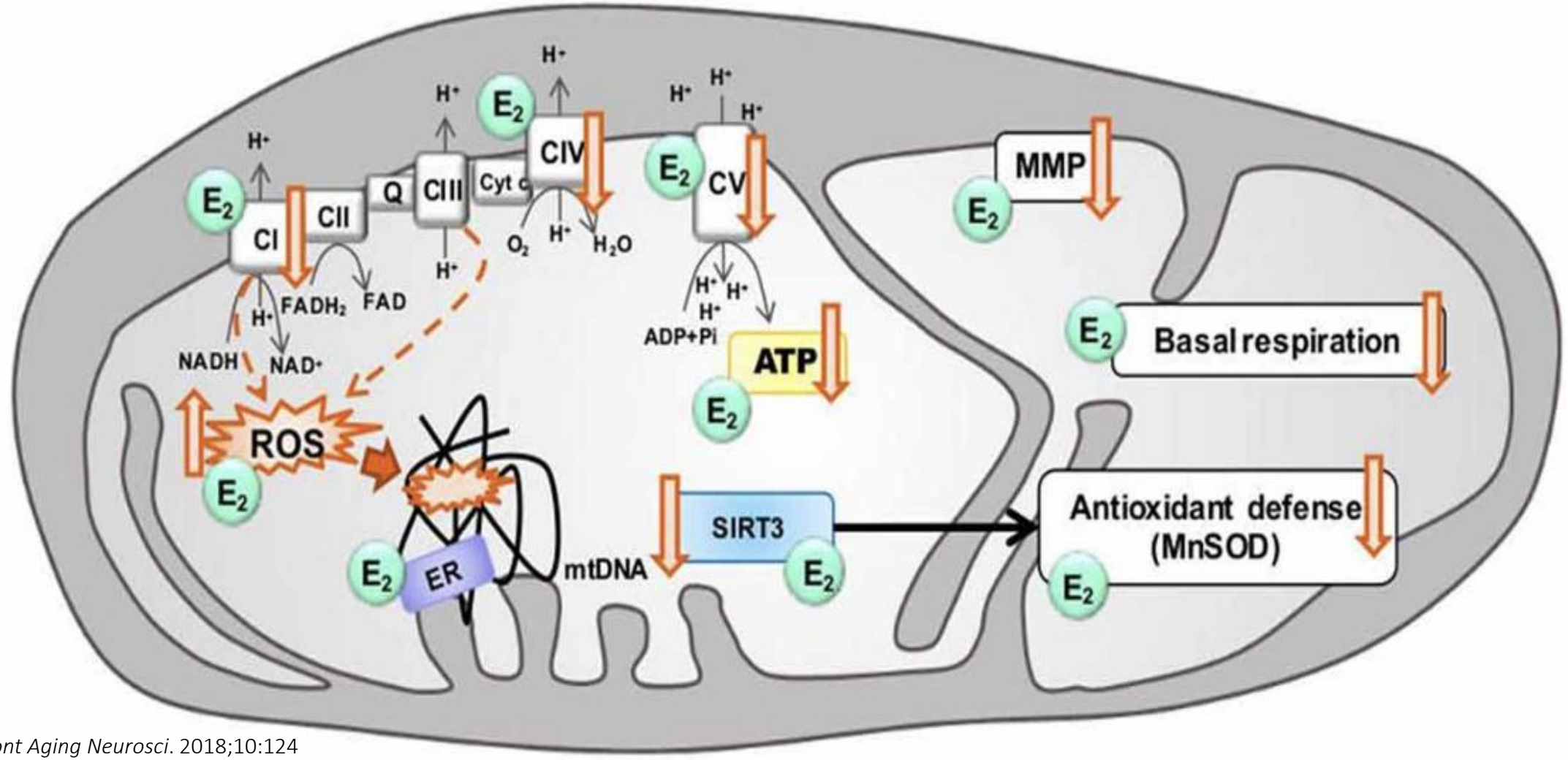
CNS Neuroscience & Therapeutics, Volume: 30, Issue: 2, First published: 09 February 2024, DOI: (10.1111/cns.14576)

Estradiol and Mitochondrial Function



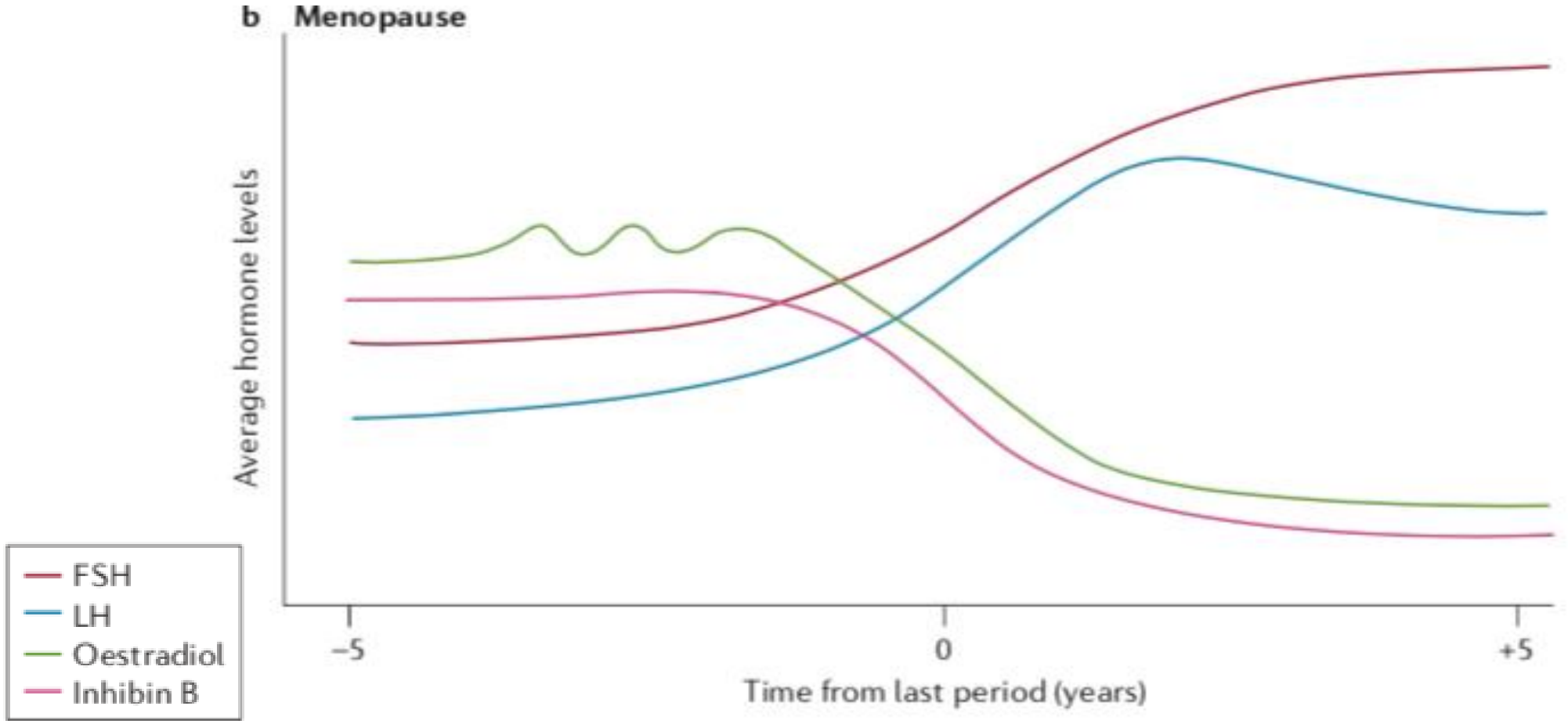
Klinge CM. Estrogenic control of mitochondrial function. Redox Biol. 2020 Apr;31:101435.

Estrogen – Mitochondria



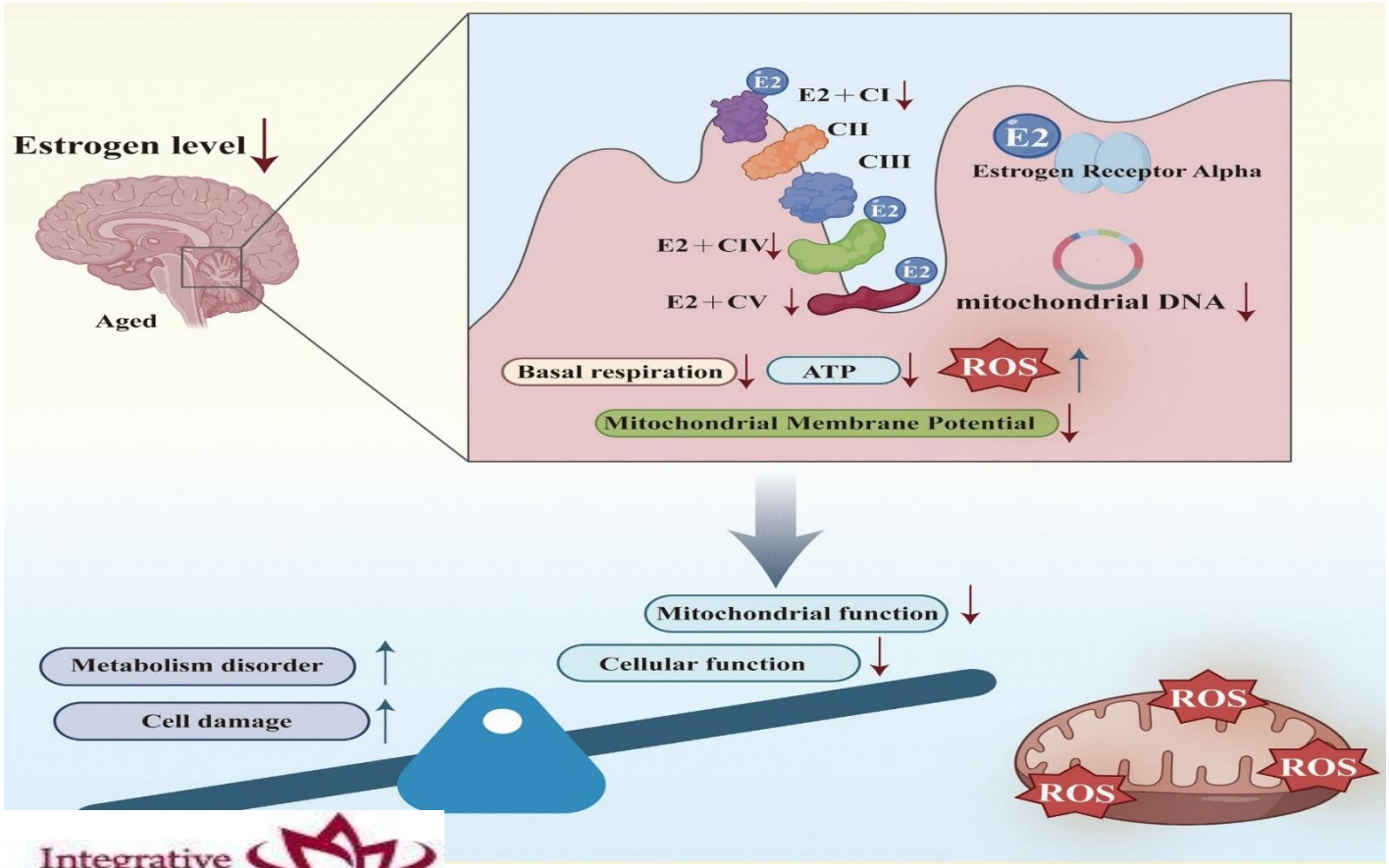
Lejri I et al. *Front Aging Neurosci*. 2018;10:124

Menopausal Hormone Changes:
Transition and Thereafter



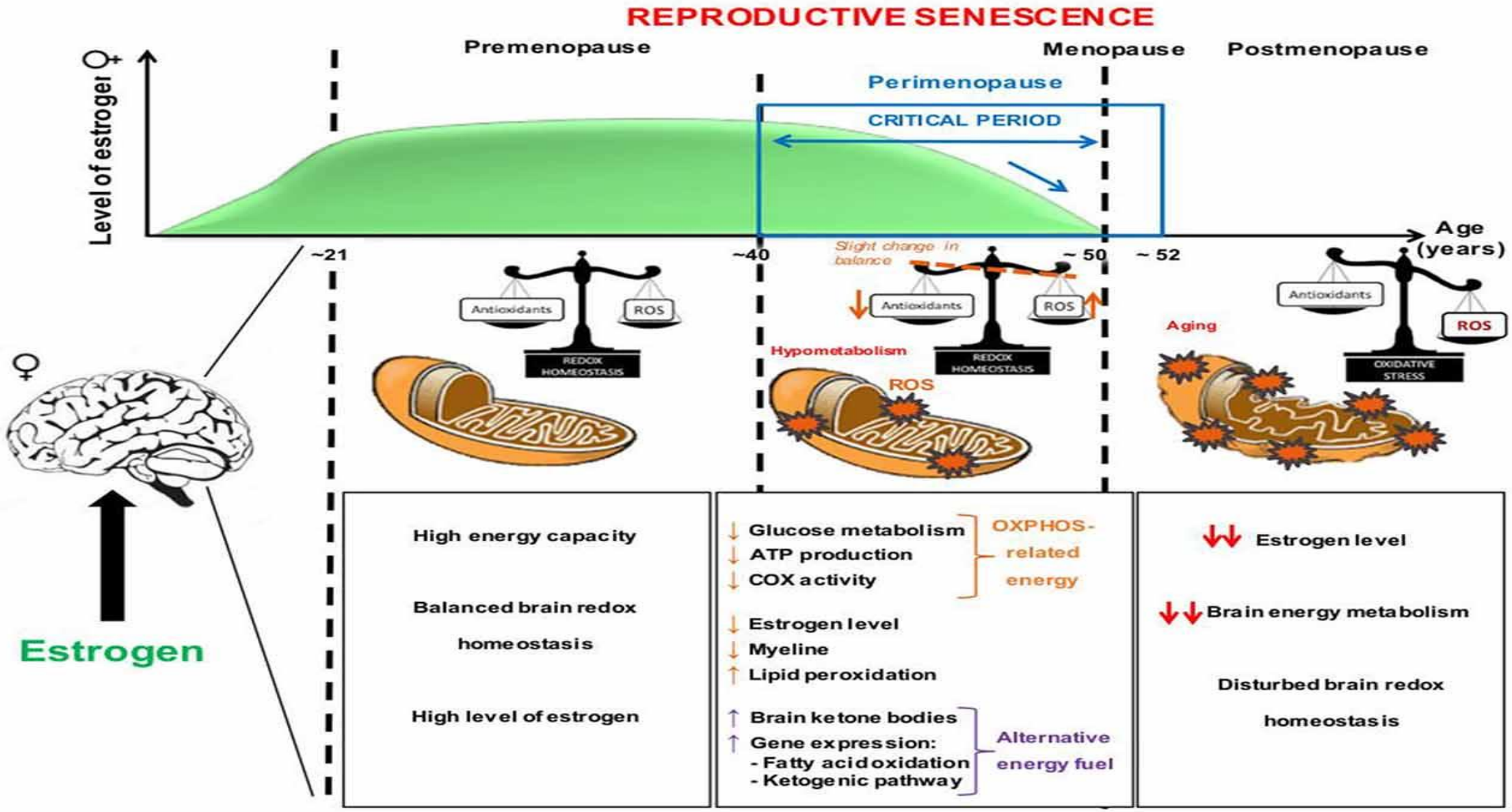
Davis, S., Lambrinoudaki, I., Lumsden, M. *et al.* Menopause. *Nat Rev Dis Primers* **1,** 15004 (2015).

Reduced Estrogen & Mitochondrial Function:

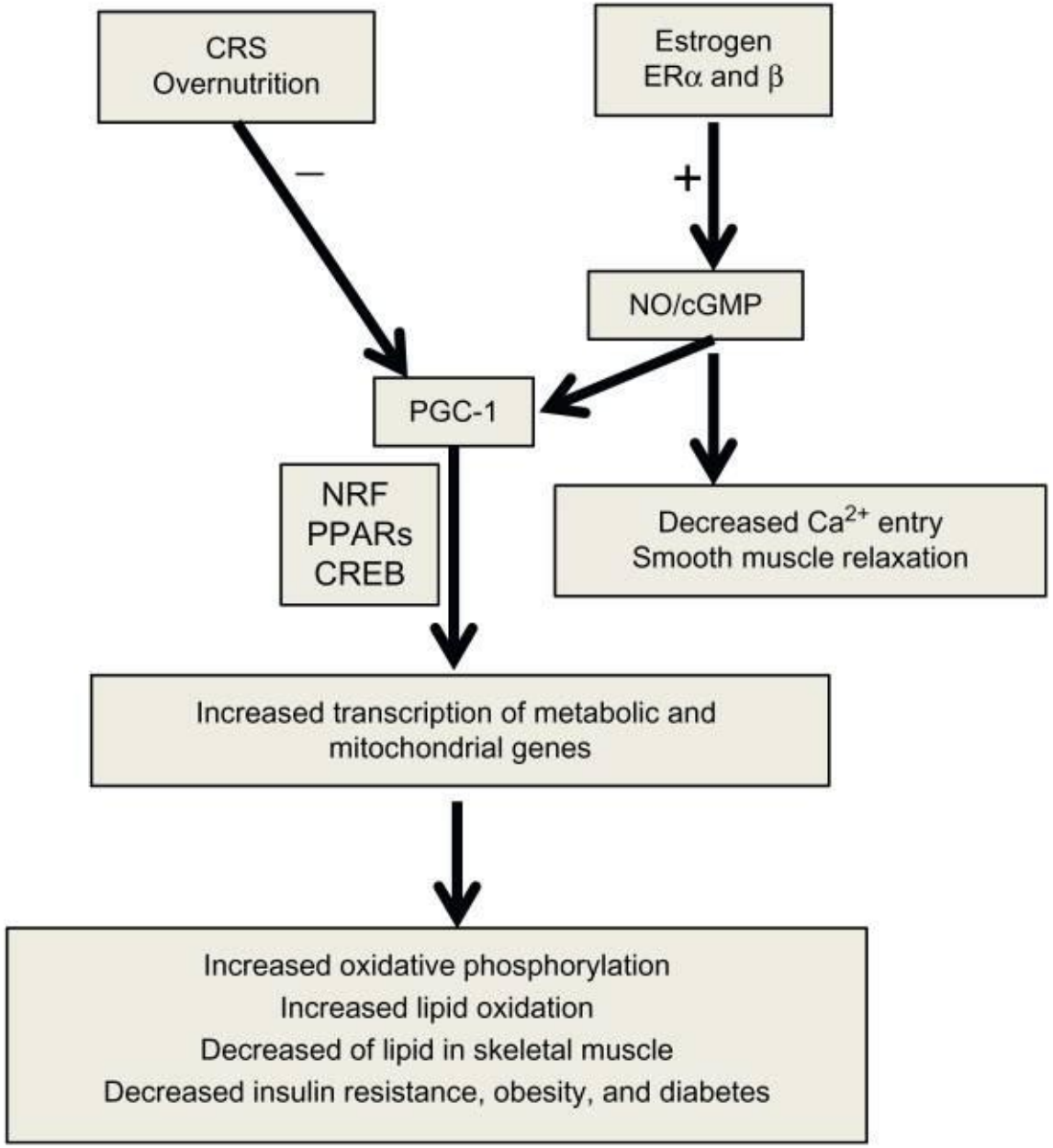


- **Reduced E2 affects mitochondrial respiratory chain complexes - reducing basal respiration, ATP production, and membrane potential - while increasing ROS generation**
- **Reduced E2 alters estrogen receptor interaction and mtDNA levels, leading to mitochondrial dysfunction, metabolic disorders, cell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

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



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

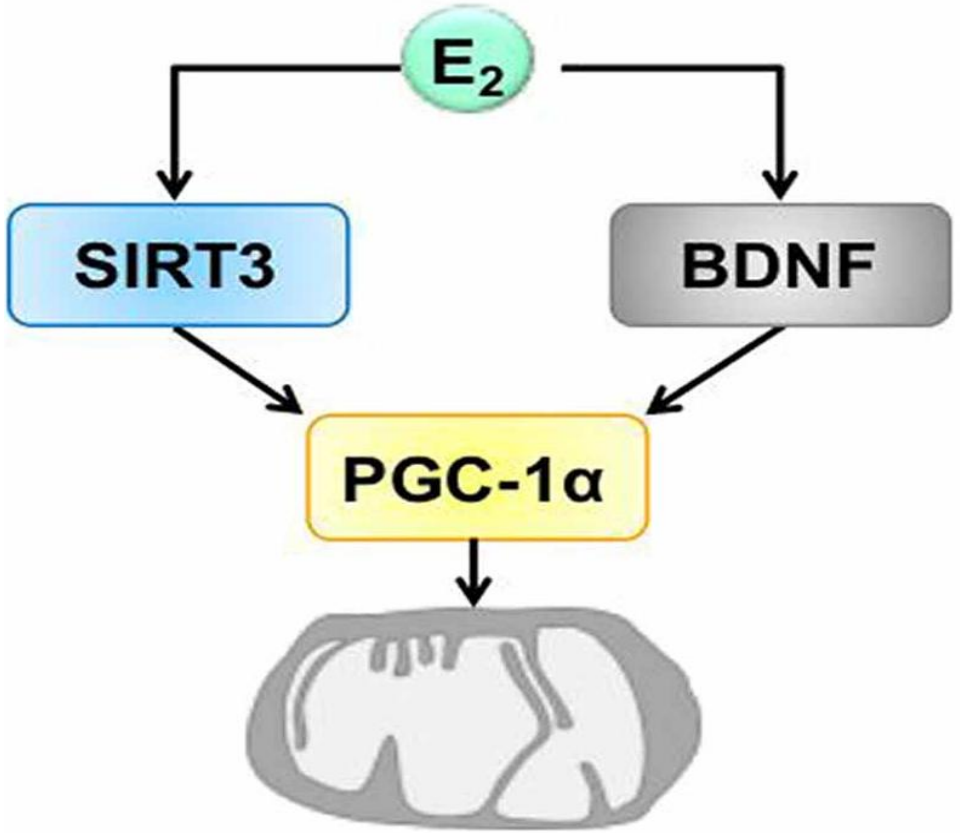


Estradiol & Mitochondrial Function

Jia G, Aroor AR, Sowers JR. Estrogen and mitochondria function in cardiorenal metabolic syndrome. Prog Mol Biol Transl Sci. 2014;127:229-49.

E2, BDNF, & SIRT3 + Mitochondria in the Brain

Estrogen (E2) induces expression of BDNF and SIRT3



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

Action BDNF & SIRT3 on mitochondria- regulates expression 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

www.frontiersin.org/articles/10.3389/fnagi.2018.00124/full

Progesterone Supports Mitochondrial Function

JES Journal of the Endocrine Society ENDOCRINE SOCIETY

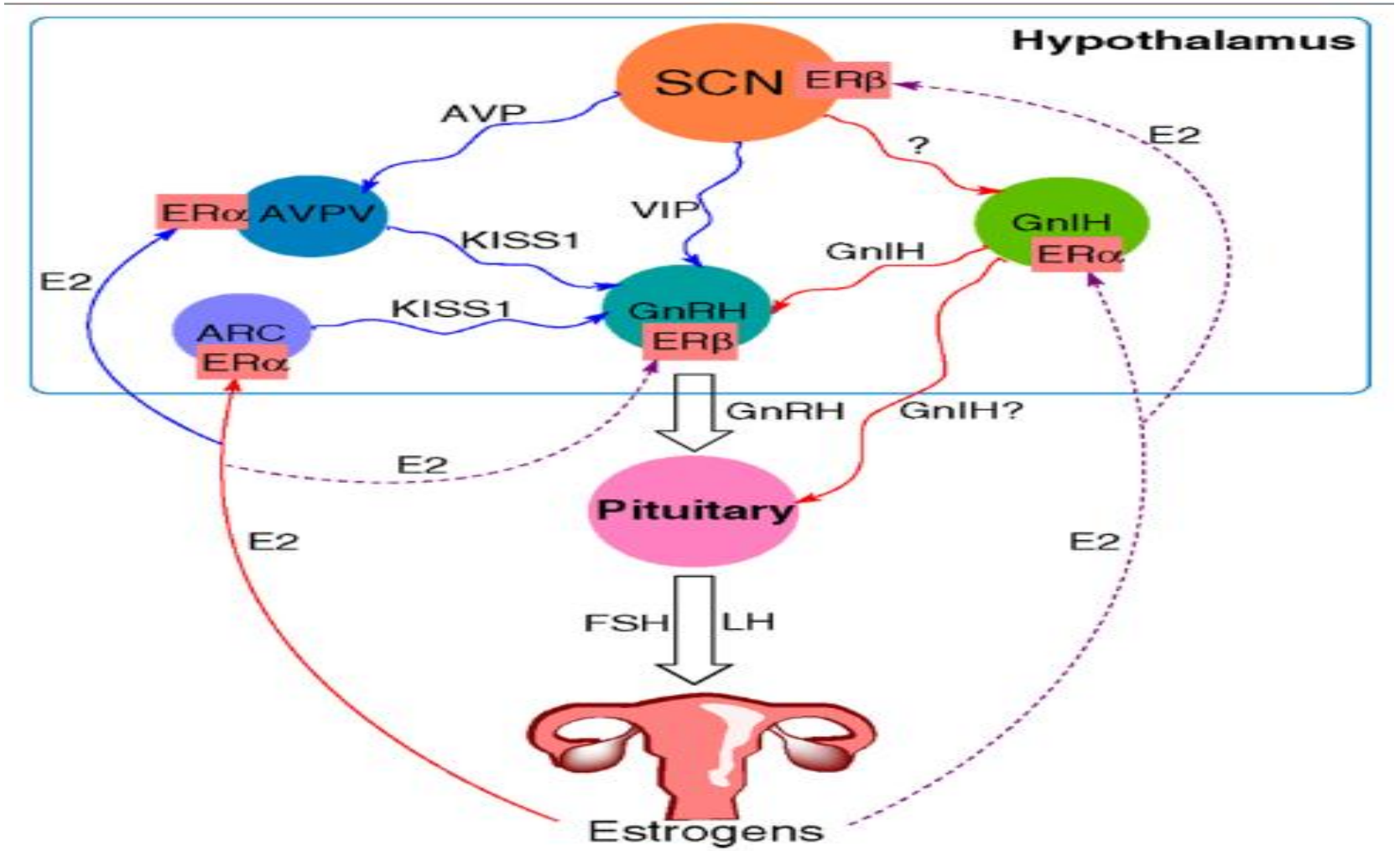
► J Endocr Soc. 2019 Jan 3;3(2):446–467. doi: 10.1210/js.2018-00219

A Mitochondrial Progesterone Receptor Increases Cardiac Beta-Oxidation and Remodeling

Qunsheng Dai [1], Creighton E Likes III [1], Anthony L Luz [2], Lan Mao [3], Jason S Yeh [1], Zhengzheng Wei [4], Maragatha Kuchibhatla [5], Olga R Ilkayeva [6], Timothy R Koves [6,7], Thomas M Price [1],

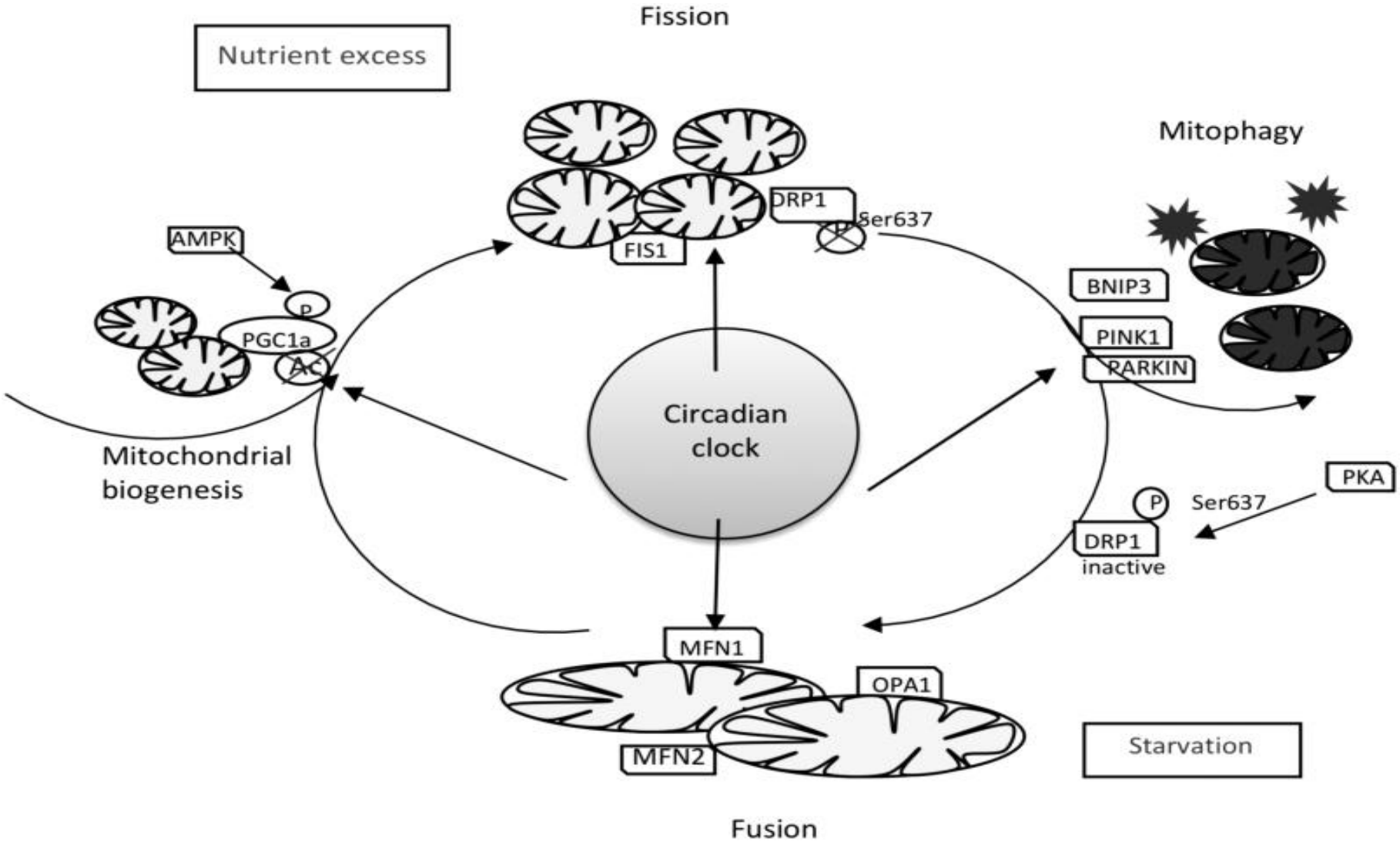
- **Boosts:**
  Cellular respiration
  Energy (ATP) production
  Membrane potential
- **Offers protection against oxidative stress & cell death (apoptosis) - brain & reproductive tissues**
- **Nuclear receptor-dependent & independent mechanisms + specific mitochondrial progesterone receptors (PR-M) identified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

Estradiol and Rhythms

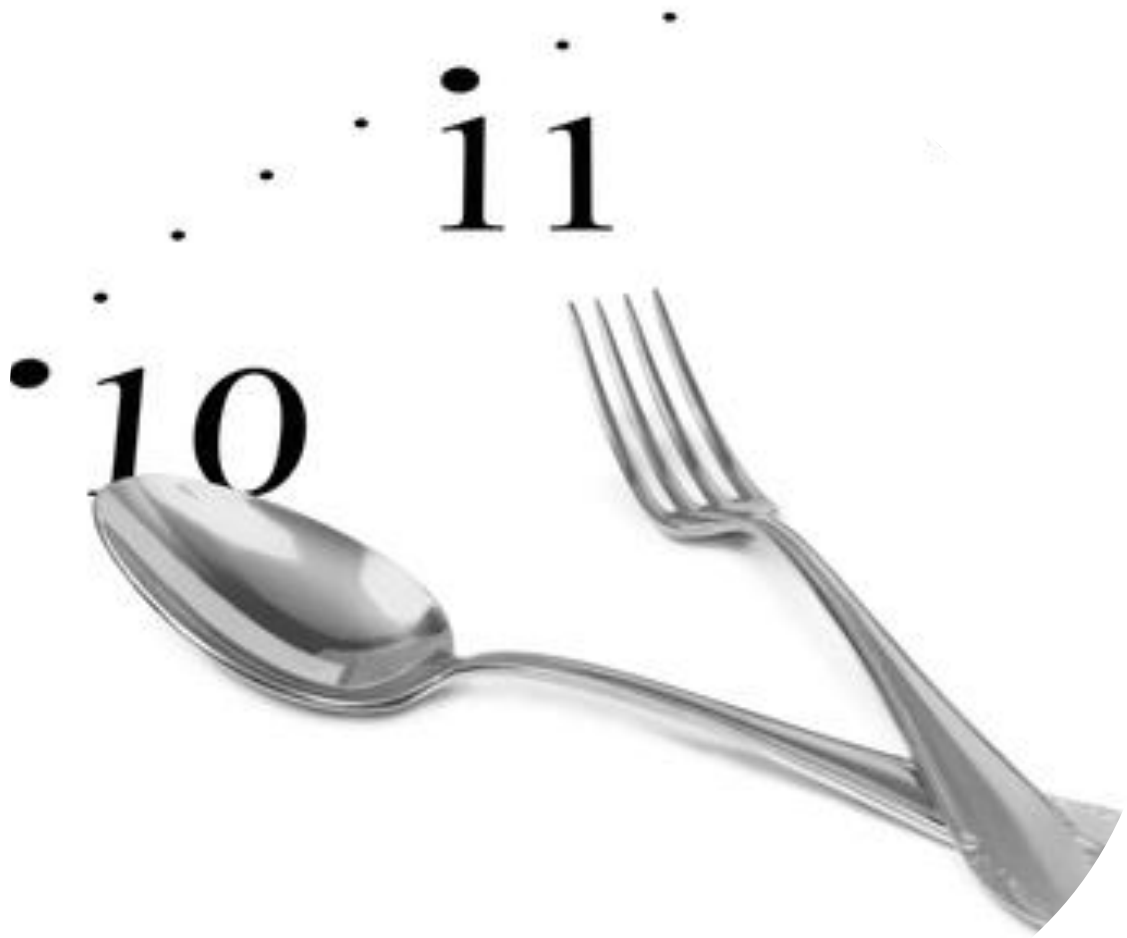


Urlep Z and Rozman D (2013) The Interplay between Circadian System, Cholesterol Synthesis, and Steroidogenesis Affects Various Aspects of Female Reproduction. Front. Endocrinol. 4:111.

The Circadian Rhythm (& Clock Genes)



Mezhnina V, Ebeigbe OP, Poe A, Kondratov RV. Circadian Control of Mitochondria in Reactive Oxygen Species Homeostasis. Antioxid Redox Signal. 2022 Oct;37(10-12):647-663.



Redefining Estrogen and Progesterone Insufficiency

It's like living a life of jetlag – and that is a major challenge!!

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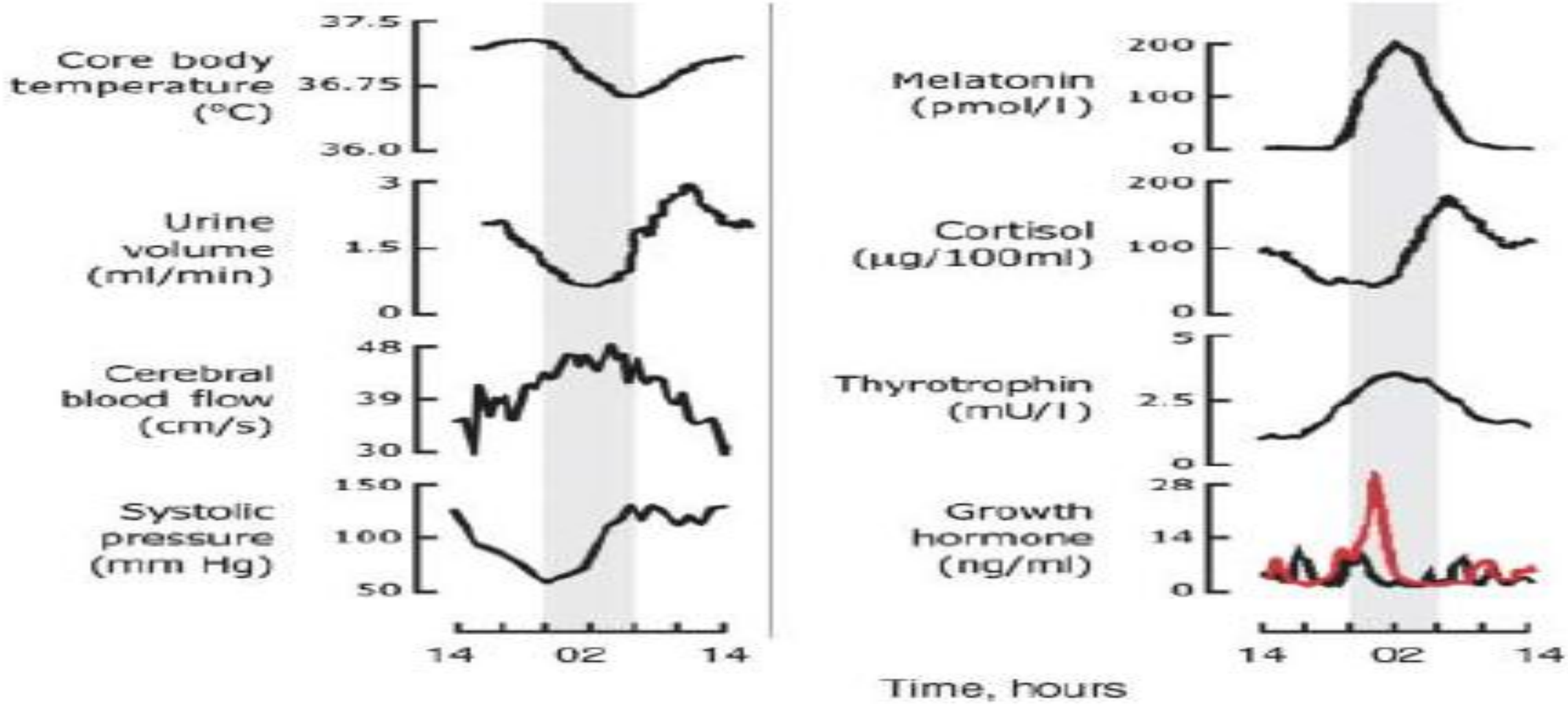
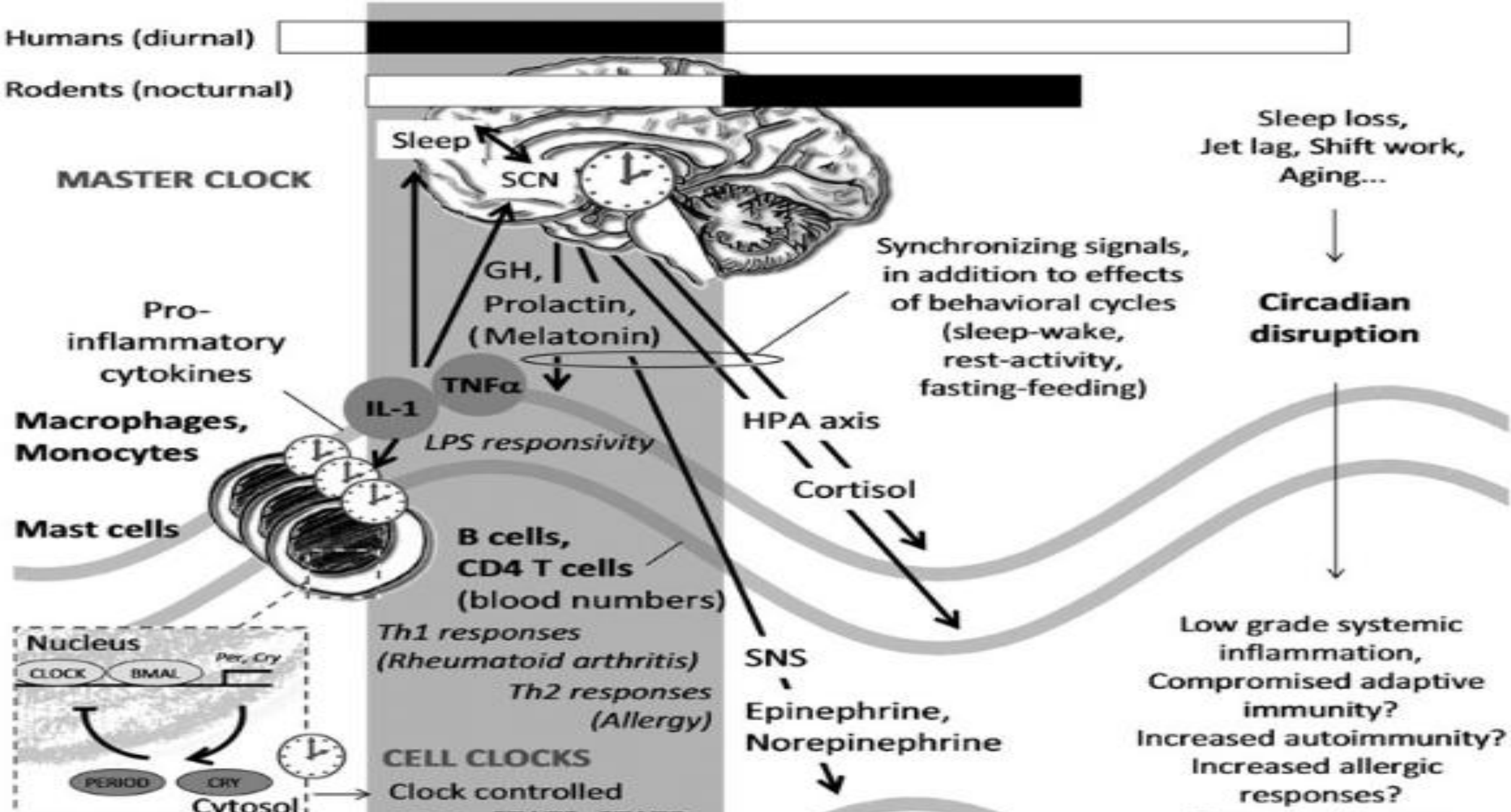
M HASTINGS and others · *Circadian clocks*



Hastings M, O'Neill JS, Maywood ES. *J Endocrinol*. 2007 Nov;195(2):187-98


Humans (diurnal)
Rodents (nocturnal)
Sleep
SCN
MASTER CLOCK
Sleep loss,
Jet lag, Shift work,
Aging...
Circadian
disruption
Synchronizing signals,
in addition to effects
of behavioral cycles
(sleep-wake,
rest-activity,
fasting-feeding)
GH,
Prolactin,
(Melatonin)
Pro-
inflammatory
cytokines
TNFα
IL-1
LPS responsivity
Macrophages,
Monocytes
Mast cells
HPA axis
Cortisol
B cells,
CD4 T cells
(blood numbers)
Th1 responses
(Rheumatoid arthritis)
Th2 responses
(Allergy)
SNS
Epinephrine,
Norepinephrine
Low grade systemic
inflammation,
Compromised adaptive
immunity?
Increased autoimmunity?
Increased allergic
responses?
Nucleus
CLOCK
BMAL
Per, Cry
PERIOD
CRY
Cytosol
CELL CLOCKS
Clock controlled

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

Estradiol Modulates Autonomic Nervous System

Clinical and Experimental Pharmacology and Physiology (2007) **34**, 827–832 doi: 10.1111/j.1440-1681.2007.04663.x

BRIEF REVIEW

ROLE OF OESTROGEN IN THE CENTRAL REGULATION OF AUTONOMIC FUNCTION

TM Saleh and BJ Connell

Department of Biomedical Science, Atlantic Veterinary College and The Prince Edward Island Health Research Institute, University of Prince Edward Island, Charlottetown, Prince Edward Island, Canada

Swartz KG et al. J Physiol. 2024;602:263-280.

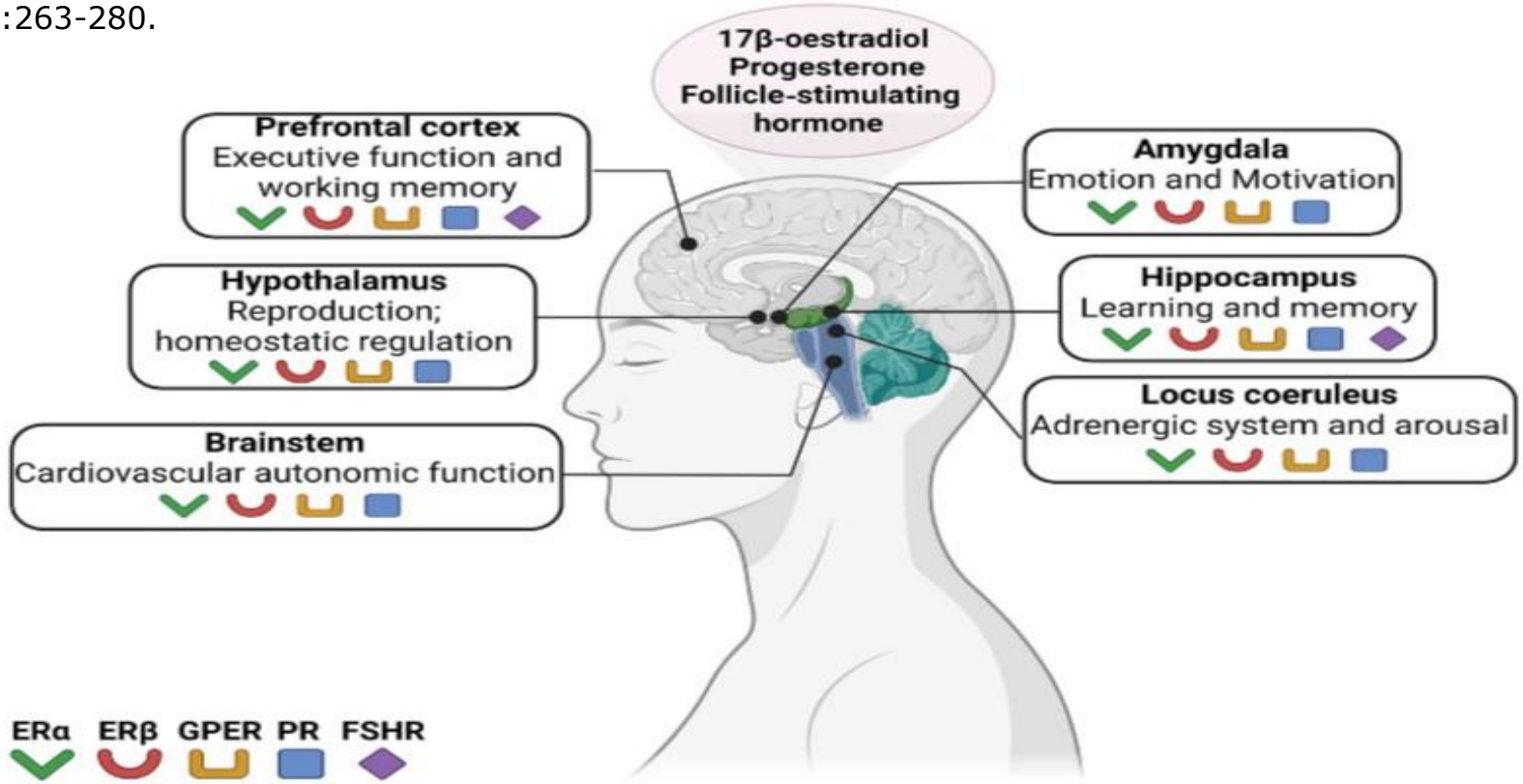
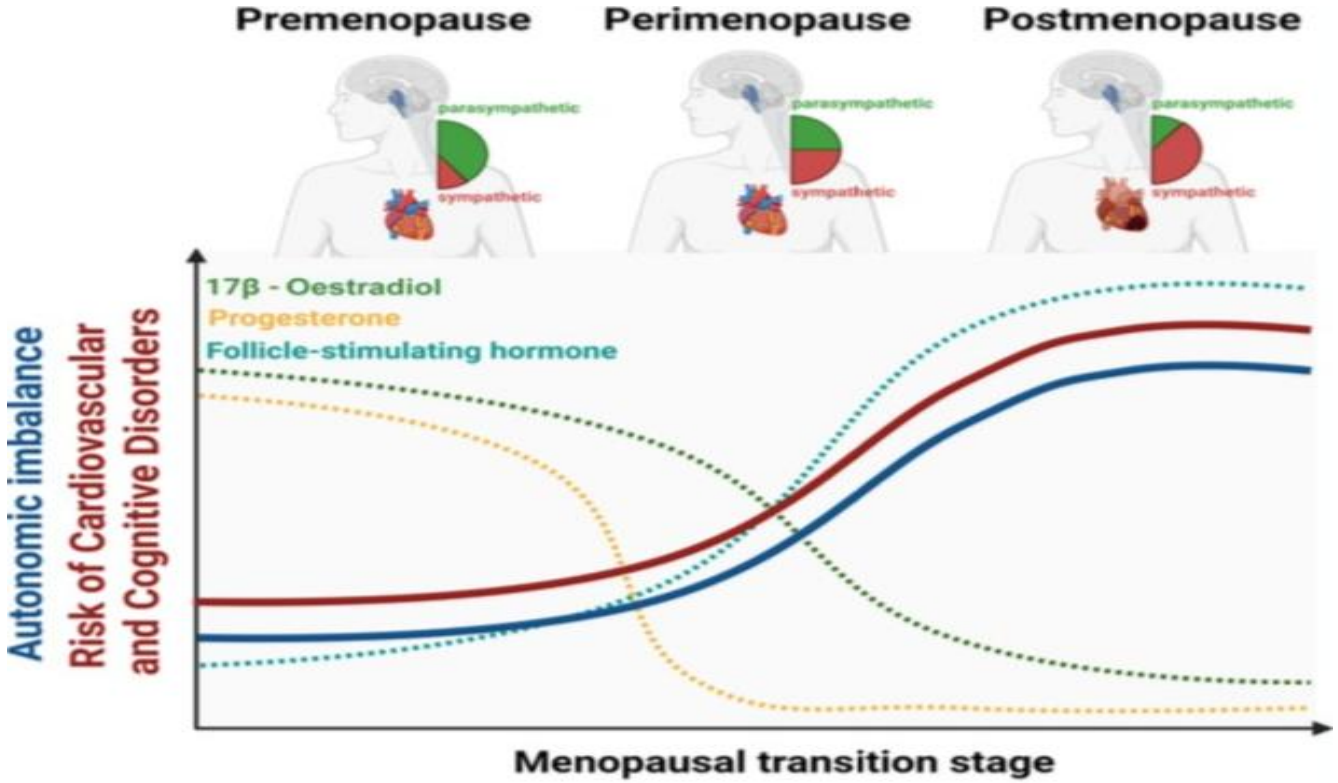


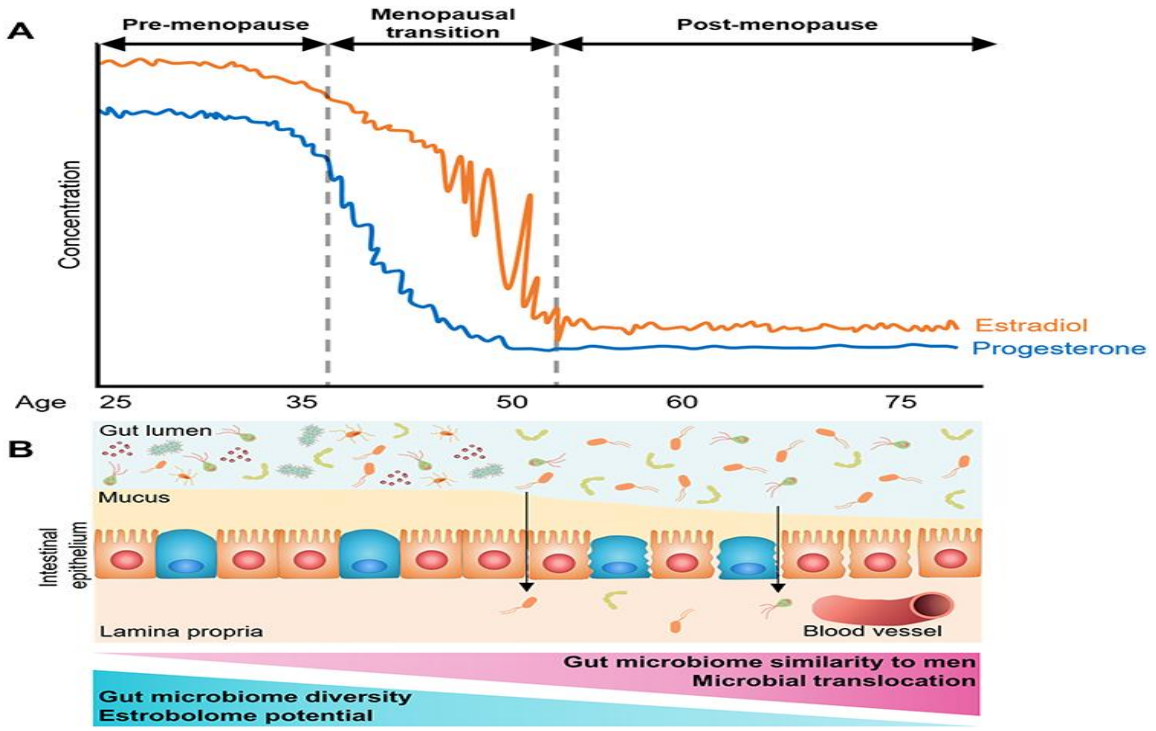
Figure 1. Reproductive hormones receptors within main brain areas related to cognitive and autonomic regulation

Oestrogen signalling has been proposed as a key modulator of women neurological function associated with learning and memory (hippocampus), executive function and working memory (cortex), emotion and motivation (amygdala), homeostatic regulation (hypothalamus), adrenergic system (locus coeruleus) and cardiovascular autonomic regulation (brainstem). A decline in oestrogen signalling may explain the symptomatology across menopause transition. Classical progesterone receptors are widely express within CNS and their activation may offer neuroprotection during aging. By contrast, evidence of neural expression of FSHR is limited and it has been related to cognitive impairment. Dysregulation of central hormonal signalling, either through changes in circulating oestrogen, progesterone and/or FSH or through modifications of receptors expression, will affect complex neural circuits. ERα, oestrogen receptor alpha; ERβ, oestrogen receptor beta; GPER, G protein-coupled oestrogen receptor; PR, progesterone receptor; FSHR, follicle-stimulating hormone receptor.

Hormone Levels and the Menopausal Transition/Menopause:

The Autonomic Nervous System and the Gut Microbiome





Swartz KG et al. J Physiol. 2024;602:263-280.

Peters BA, Santoro N, Kaplan RC, Qi Q. Spotlight on the Gut Microbiome in Menopause: Current Insights. *Int J Womens Health*. 2022;14:1059-1072

Circadian Rhythms:

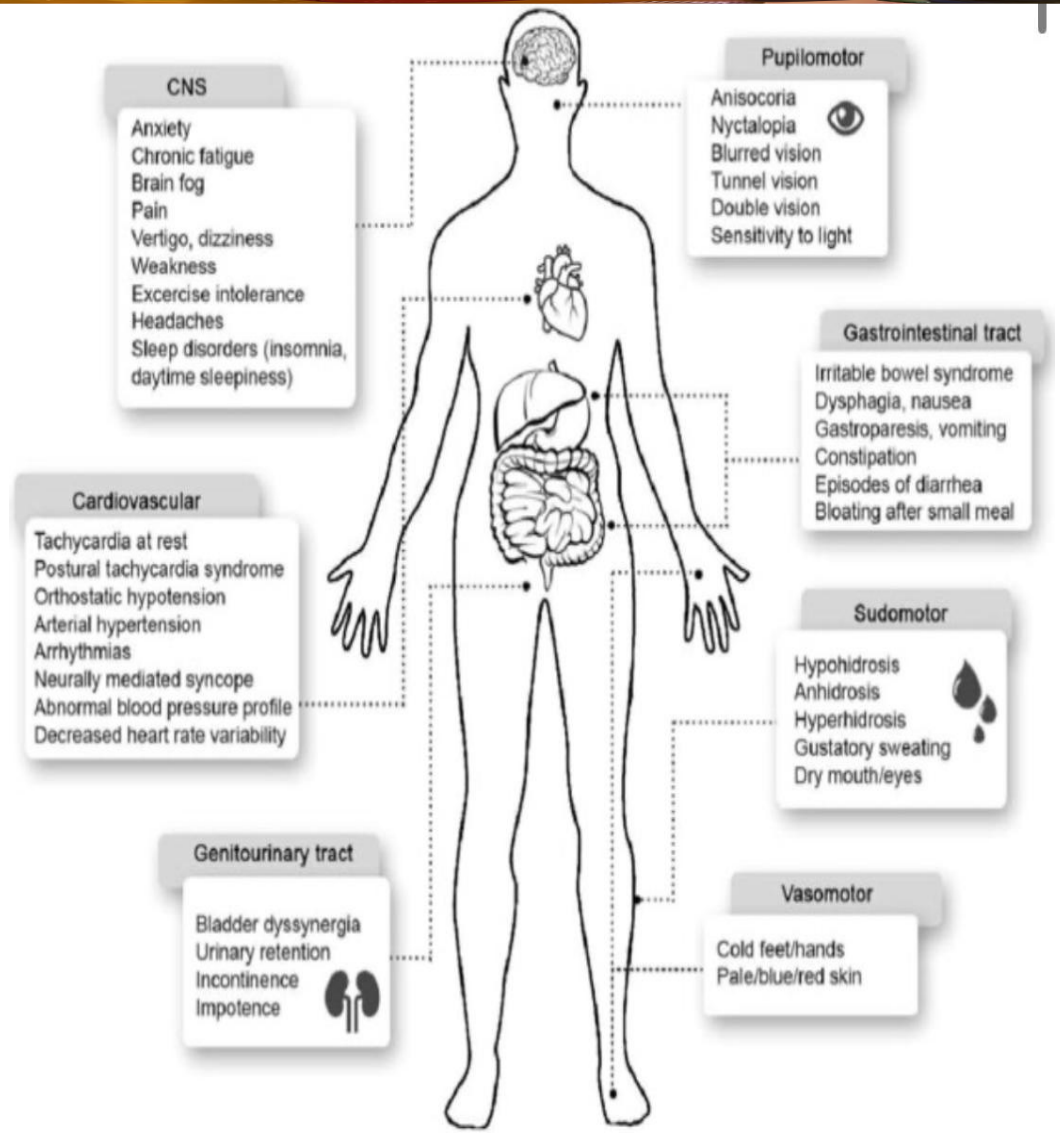
Regulate physiological functions - autonomic activity

Autonomic dysfunction and chronic disease

Nov 2018 · British Medical Bulletin 128(1)

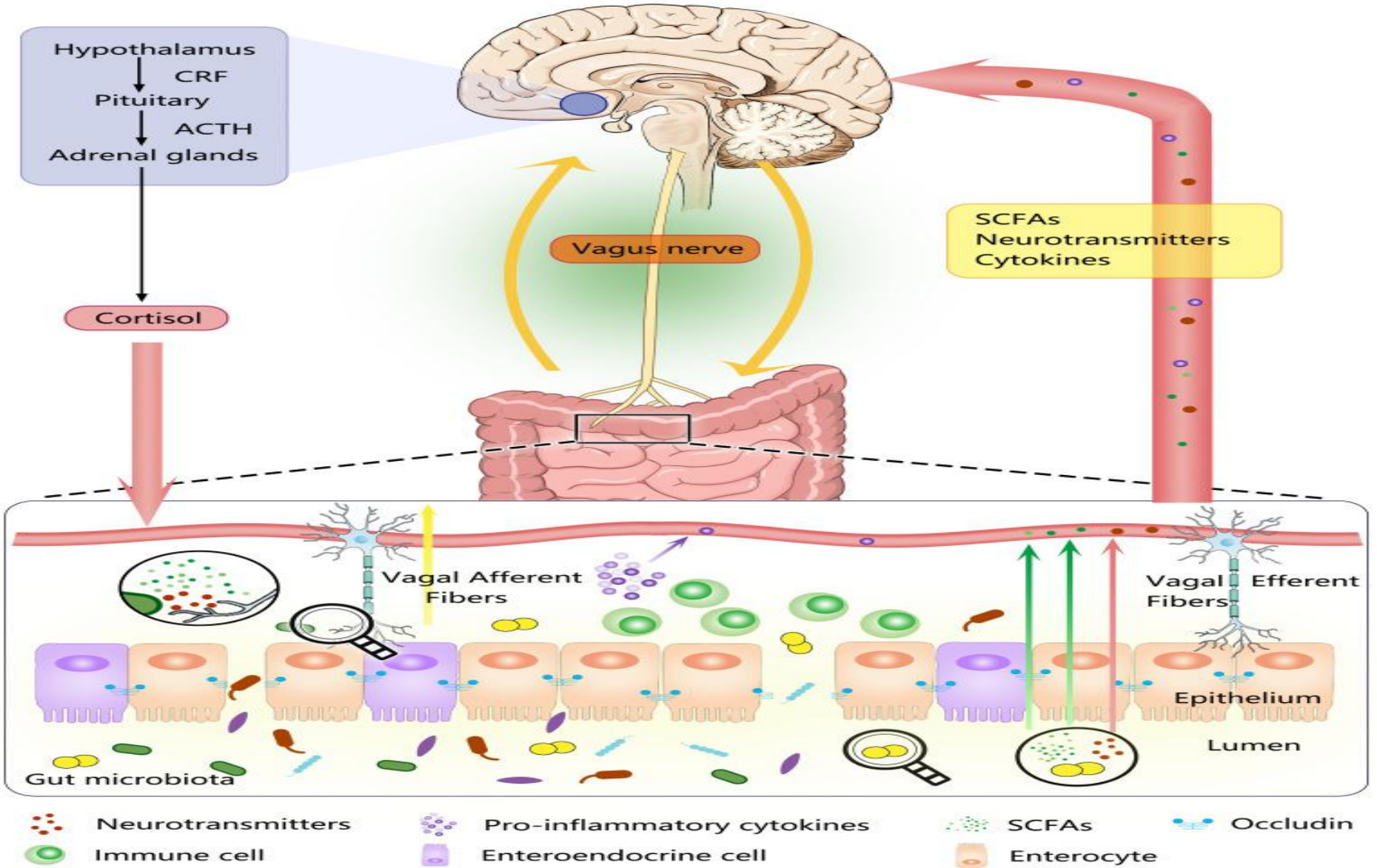
DOI: 10.1093/bmb/ldy036

Pawel Zalewski · Joanna Słomko ·
Monika Zawadka-Kunikowska

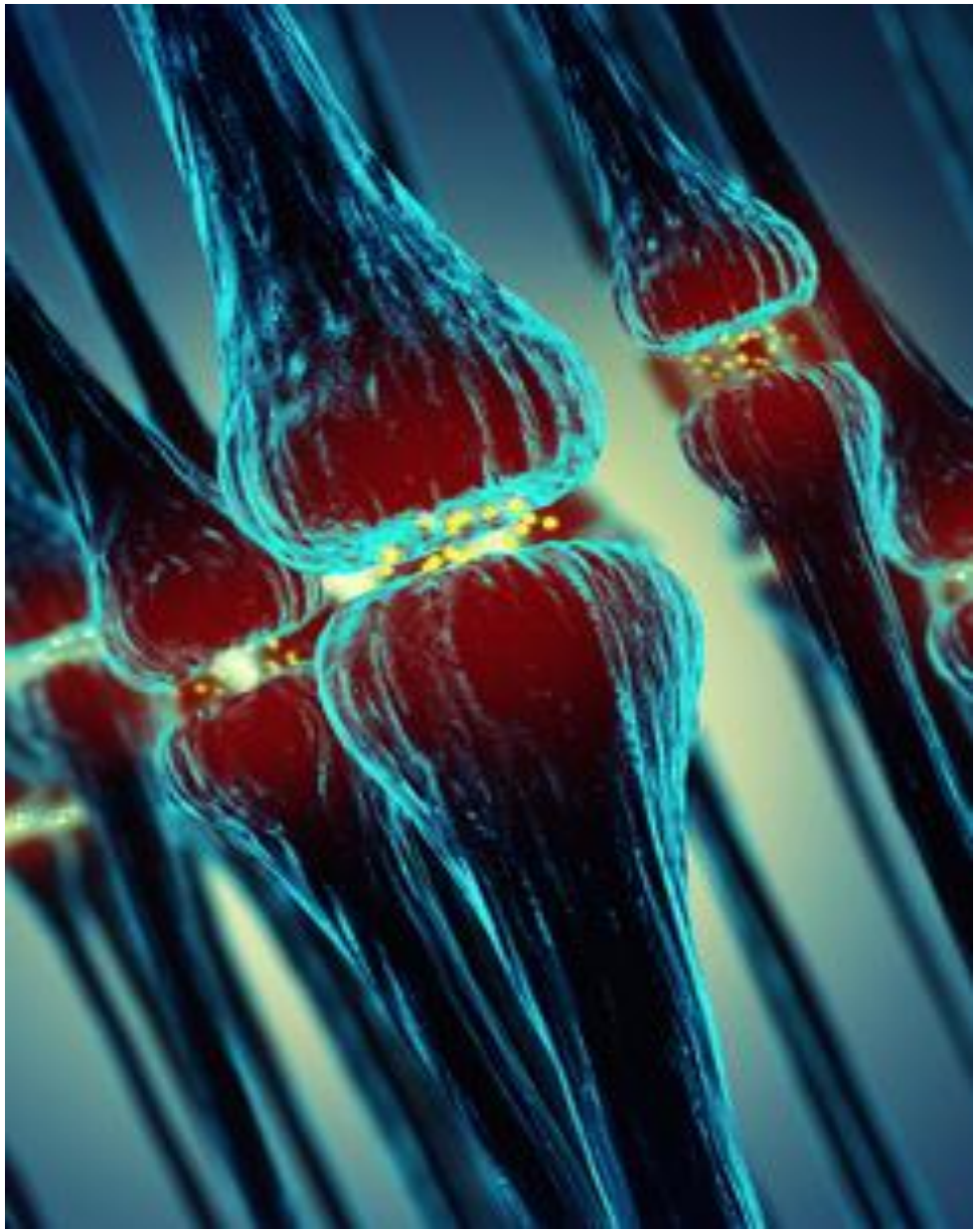


Chapter 28 - Circadian rhythms and autonomic functionDiego A. Golombék, Daniel E. Vigo,
Editor(s): Italo Biaggioni, Kirsteen Browning, Gregory Fink, Jens Jordan, Phillip A. Low, Julian F.R. PatonPrimer on the Autonomic Nervous System (Fourth Edition),
Academic Press,2023, Pages 161-164

Linking the Autonomic Nervous System and the Gut Microbiome



Cryan JF et al. The Microbiota-Gut-Brain Axis. Physiological Reviews. 2019 online



Estrogen-Cholinergic Interactions

- Important site of action for estrogen in brain is cholinergic system
- Critical role of CNS cholinergic systems in cognition
- Basal forebrain cholinergic systems dependent on estradiol support for adequate functioning

Estradiol & Dopamine

Almey et al. Horm Behav.2016;74:125-138

- **Object recognition memory- dopamine-dependent cognitive process affected by estrogens**
- **Estrogens affect dopamine-dependent cognitive processes – genomic & non-genomic effects**
- **Estrogens alter dopamine function at various stages in transmission: dopamine availability, receptor density, affinity dopamine transporter**

Serotonin Neurons

Serotonin neurons modulate:

Autonomic functions

Cognitive domains

Affect/Mood

Anxiety

Stress related disorders

Estradiol supports gene expression

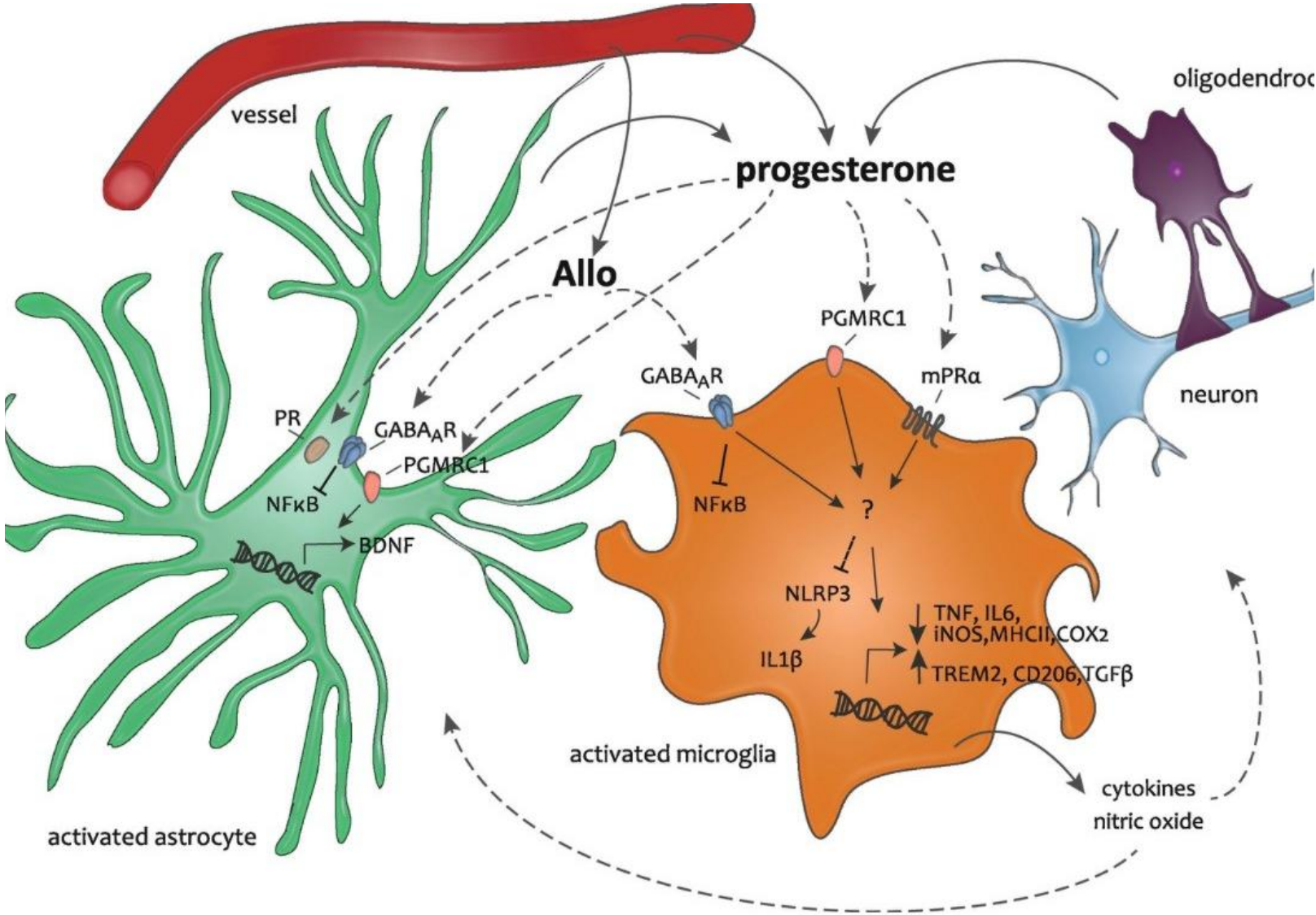
Bethea et al. Front Neuroendocrinol.2009;30(2):212-38

Frontiers in Neuroendocrinology

Volume 55, October 2019, 100788

Neurosteroids as regulators of neuroinflammation

Canelif Yilmaz [a 1], Kanelina Karali [b c 1], Georgia Fodelianaki [a], Achille Gravanis [b c], Triantafyllos Chavakis [a d], Ioannis Charalampopoulos [b c], Vasileia Ismini Alexaki [a]



What do We Do?

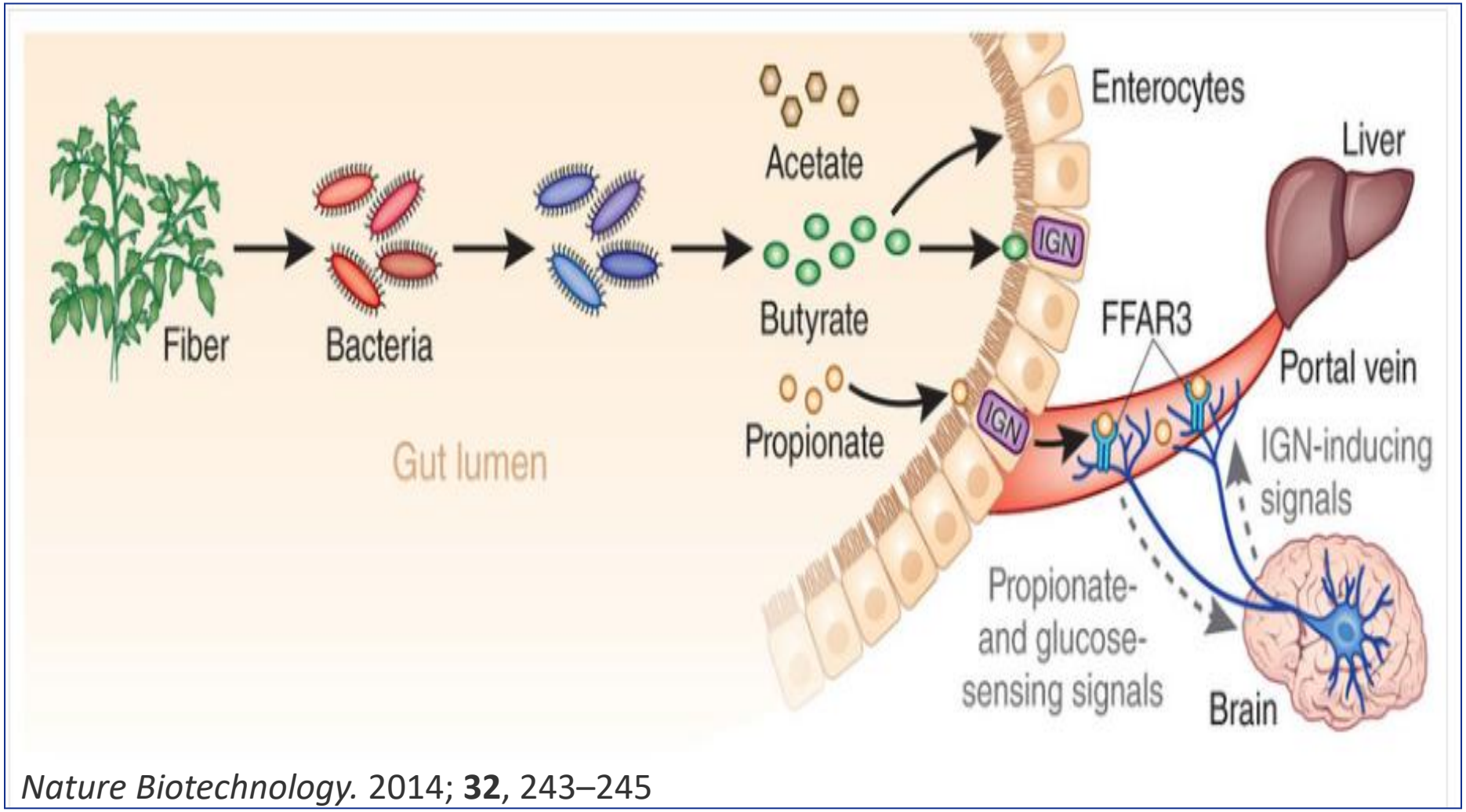
Optimization of Mitochondrial - Metabolic - Brain Health

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

Hormone Therapy

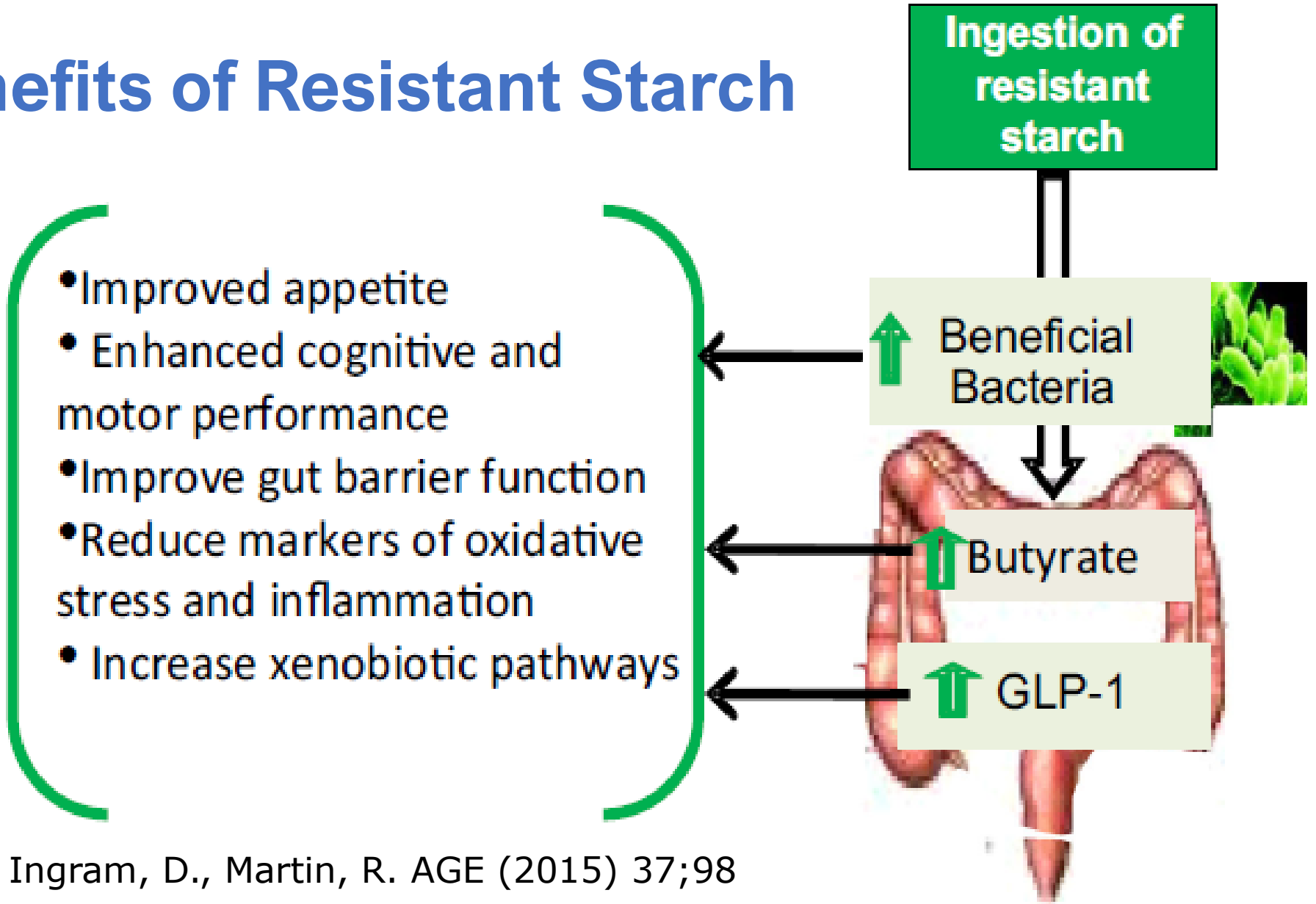
The Gut Microbiome & Short Chain Fatty Acids:

Metabolic and Emotional Health



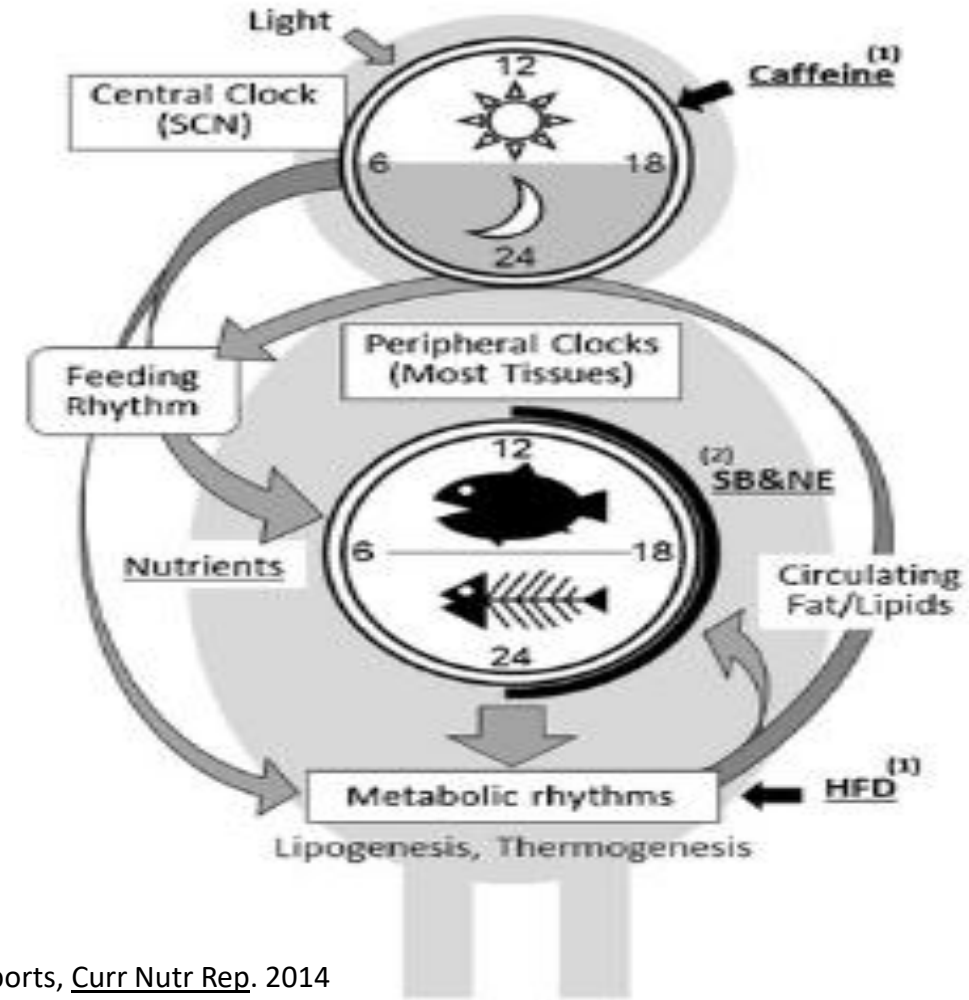
Nature Biotechnology. 2014; **32**, 243–245

Benefits of Resistant Starch



Keenan, M., Marco, M., Ingram, D., Martin, R. AGE (2015) 37;98

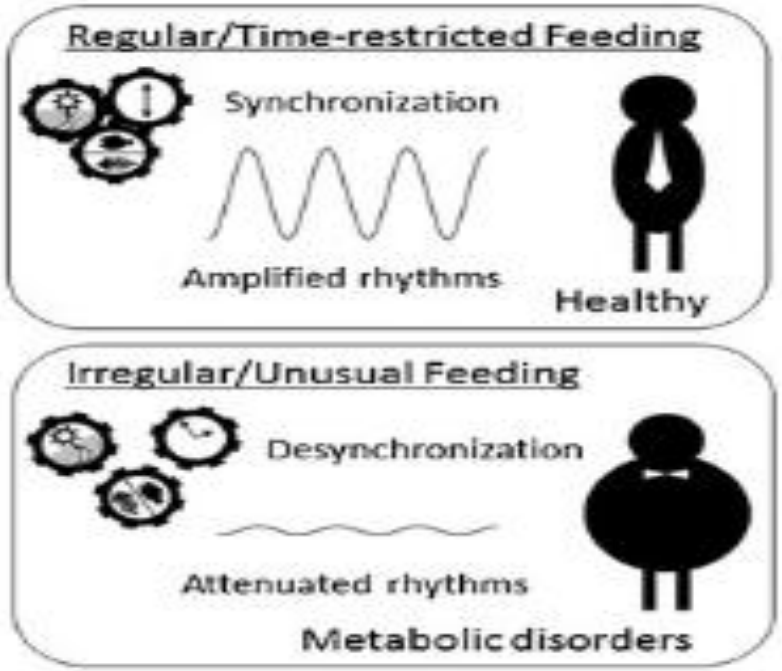
Circadian Rhythm + Time Restricted Eating for Metabolic Health



Chrono-nutrition

(1) Clock regulation
ex. High-fat diet (HFD), Caffeine

(2) Meal-time effects
ex. Skipping breakfast (SB)
Nocturnal eating (NE)



Current Nutrition Reports, Curr Nutr Rep. 2014

Anti-Stress/NS Effects of Timed Eating

Short term (12 hour) fasting during luteal phase of young women resulted in:

- **Higher parasympathetic activity**
- **Lower salivary cortisol levels**

Ohara et al. BMC Womens Health. 2015;15:67

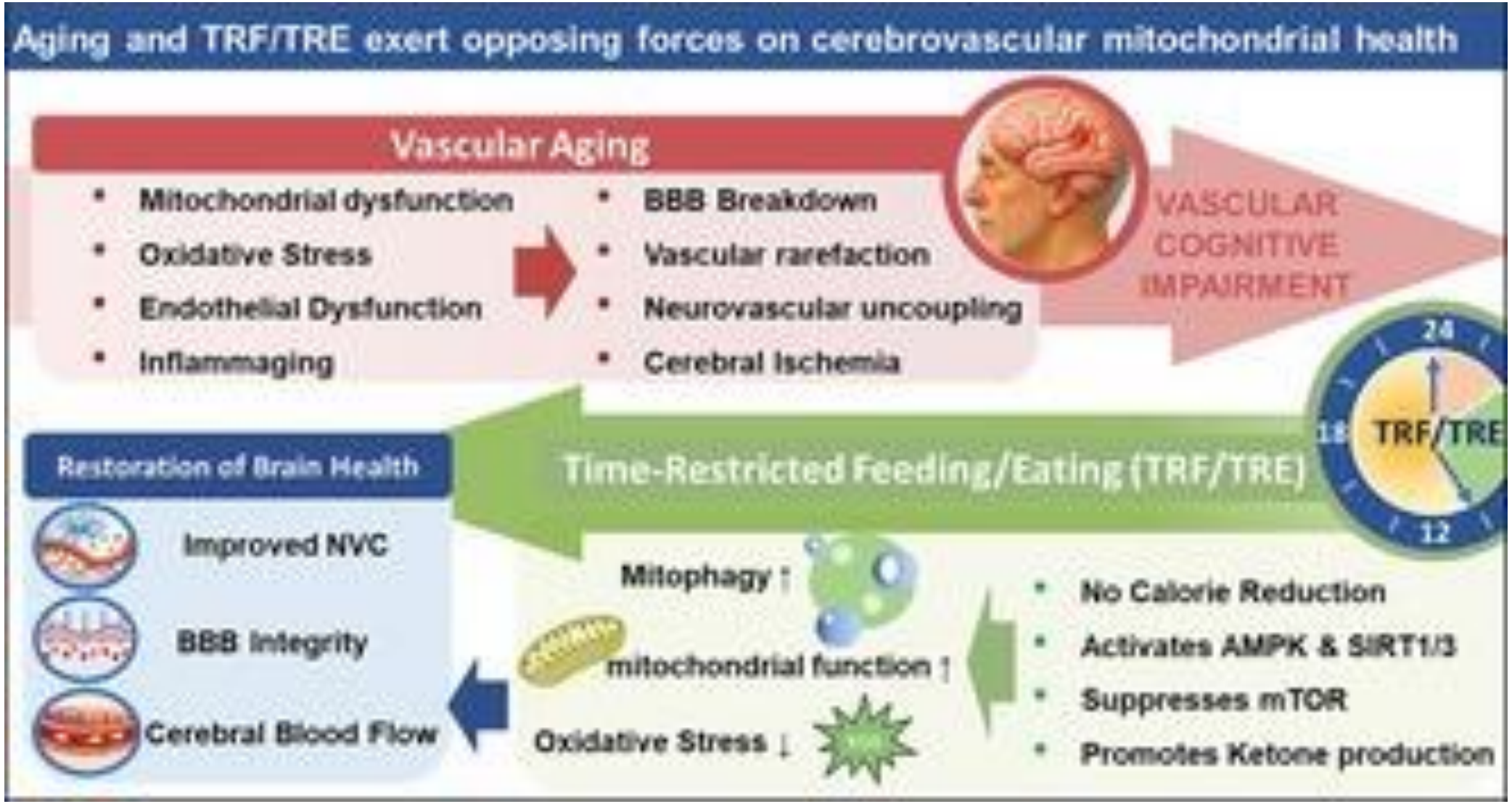
Mitochondrial Rejuvenation Approaches:

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
Probiotics & Prebiotics
Support Circadian Rhythm
Adrenal adaptogens
Exercise
Socializing

Mitochondrial Rejuvenation for Brain Health



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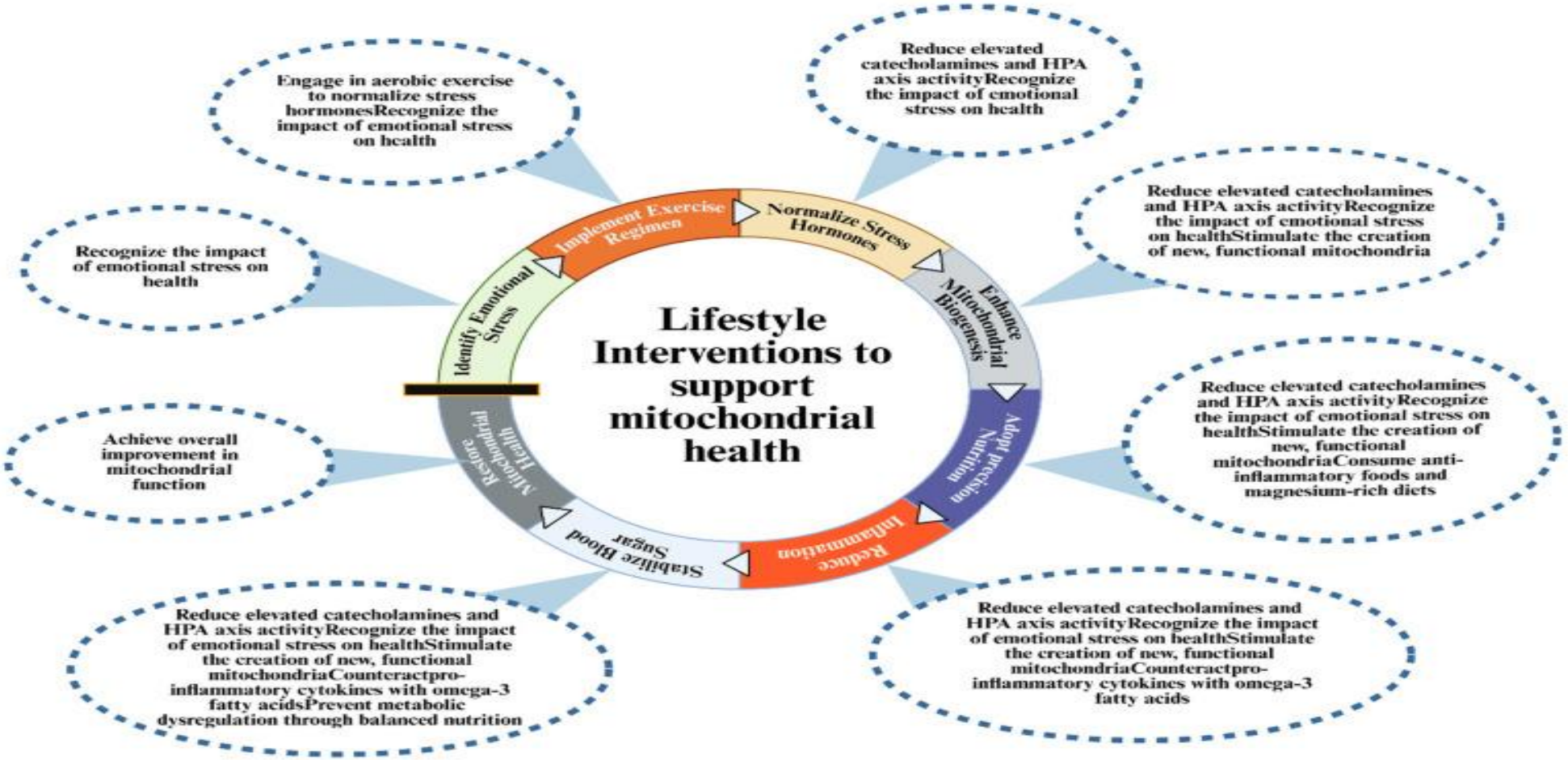
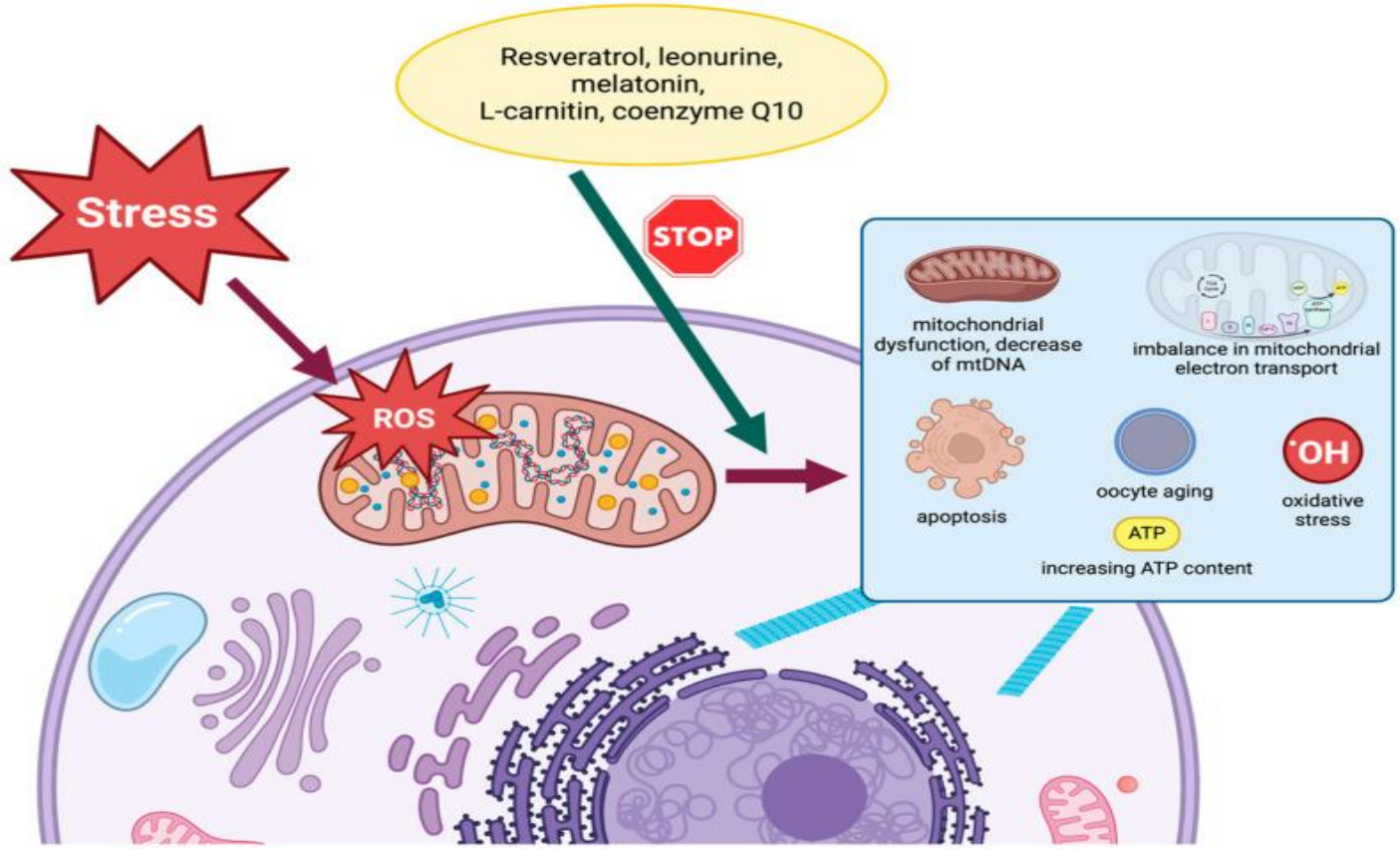
Milan M, Troyano-Rodriguez E, Ihuoma J, Negri S, Rudraboina R, Kosmider A, Awasthi S, Balasubramanian P, Conley S, Yabluchanskiy A, Csiszar A, Ungvari Z, de Cabo R, Tarantini S. Fasting as Medicine: Mitochondrial and Endothelial Rejuvenation in Vascular Aging. Aging Cell. 2026 Feb;25(2):e70372.

Lifestyle Interventions:
Support Mitochondrial Health



Venkatesan S, Comi C, De Marchi F, Esposito T, Gramaglia C, Smirne C, Ola Pour MM, Pirisi M, Vaschetto R, Zeppegno P, Grossini E. Mitochondrial Dysfunction: The Cellular Bridge from Emotional Stress to Disease Onset: A Narrative Review. Biomolecules. 2026 Jan 8;16(1):117.

Beneficial Effects of Different Substances on Mitochondrial Functions



Gałęska E, Kowalczyk A, Wrzecińska M, García MC, Czerniawska-Piątkowska E, Gwoździewicz 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.

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
- Spermadine
- Melatonin
- L Carnitine
- Probiotics
- Omega 3
- Repair Gut Microbiome Support
- Magnesium

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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

Mitochondria and Melatonin

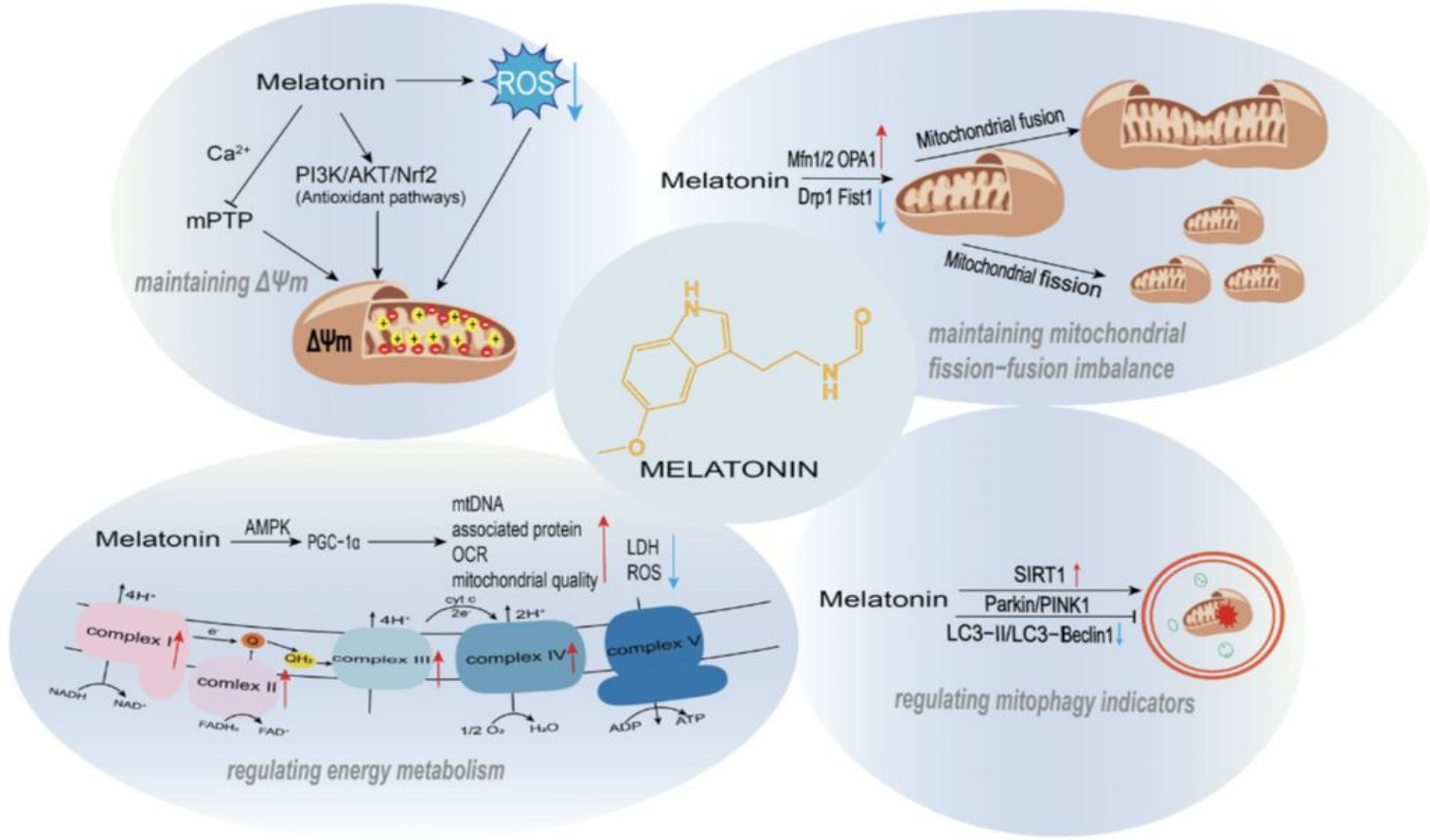
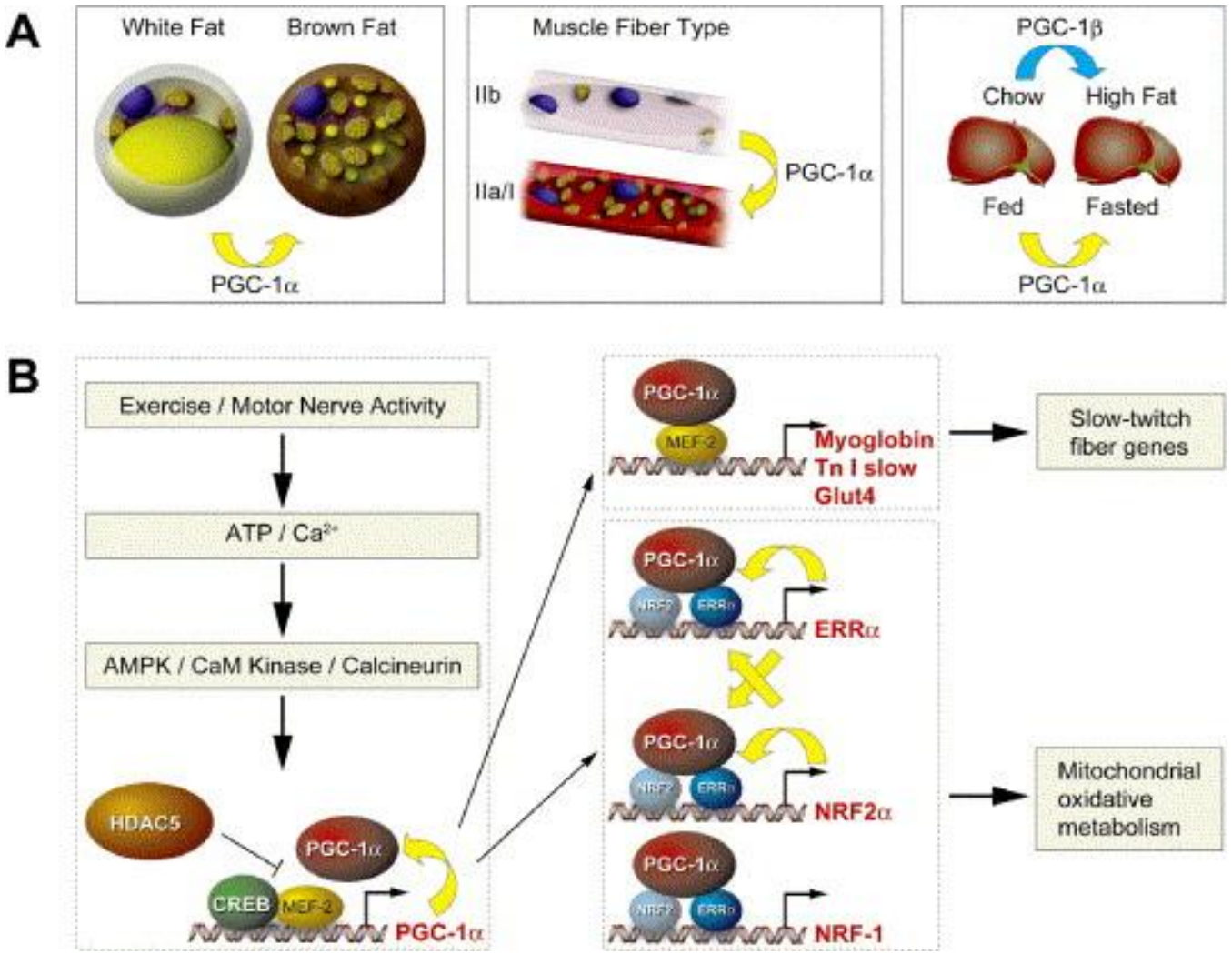


Figure 2. The regulatory roles of melatonin in mitochondrial function. Melatonin supports mitochondrial homeostasis through multiple mechanisms, including the maintenance of mitochondrial membrane potential, regulation of mitochondrial quality control, promotion of mitochondrial biogenesis, and modulation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

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

Exercise and Mitochondrial Function



Exercise (specifically HIIT) improves insulin sensitivity & mitochondrial capacity

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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

Zhang, J., Bao, Y., Zhou, X. *et al.* Polycystic ovary syndrome and mitochondrial dysfunction. *Reprod Biol Endocrinol* **17**, 67 (2019).

General Overview of Supplement Protocols

Sleep

- Melatonin
- Ashwaganda
- L-theanine
- Magnesium
- CBD
- GABA

Immune balance

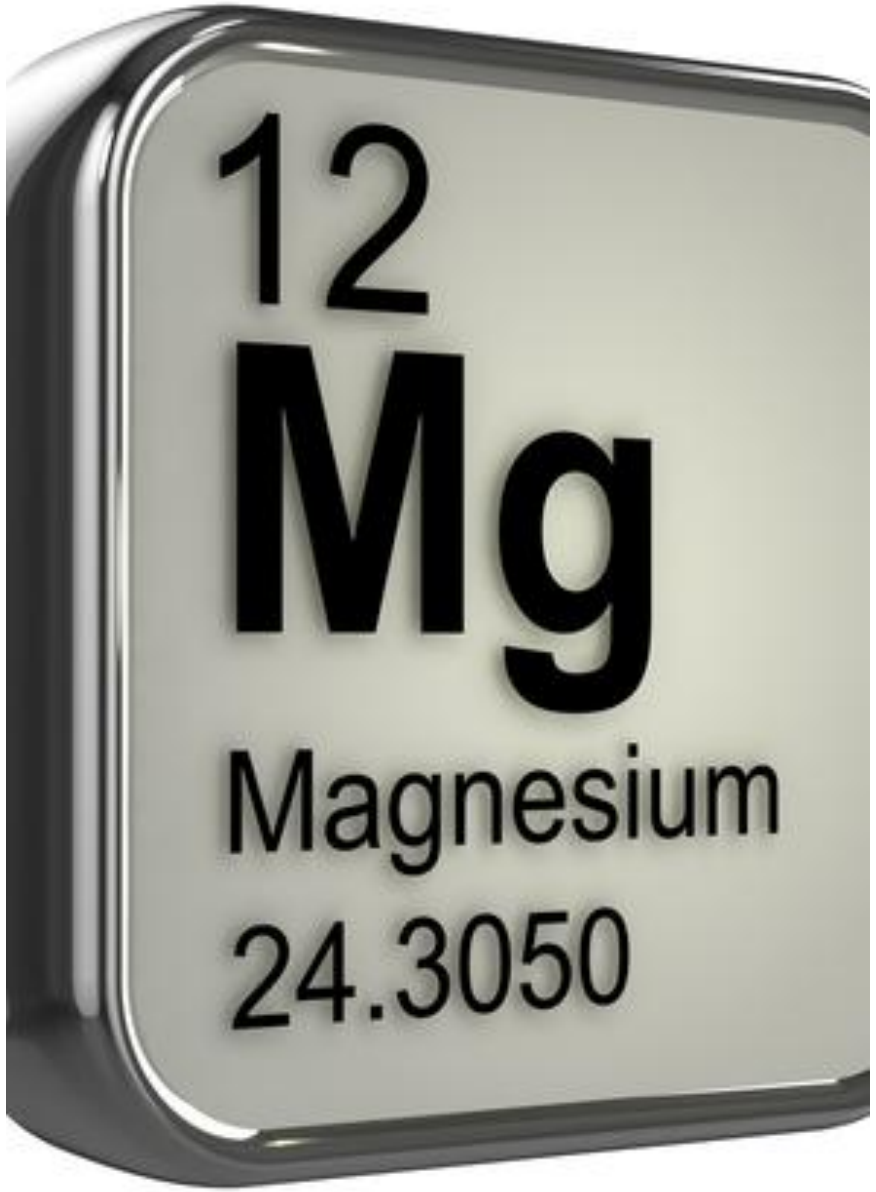
- Fish Oil – Omega 3
- Vitamin D
- Quercetin
- NAC
- Zinc
- Ginger
- Probiotic

Cognition and Mood

- Curcumin
- Ubiquinol/COQ10
- Rhodiola
- Bacopa
- Magnesium
- Saffron
- Urolithin a
- NMN (NAD+)

Insulin function

- Curcumin
- Chromium
- Berberine



Magnesium

Essential roles in over 700 reactions:

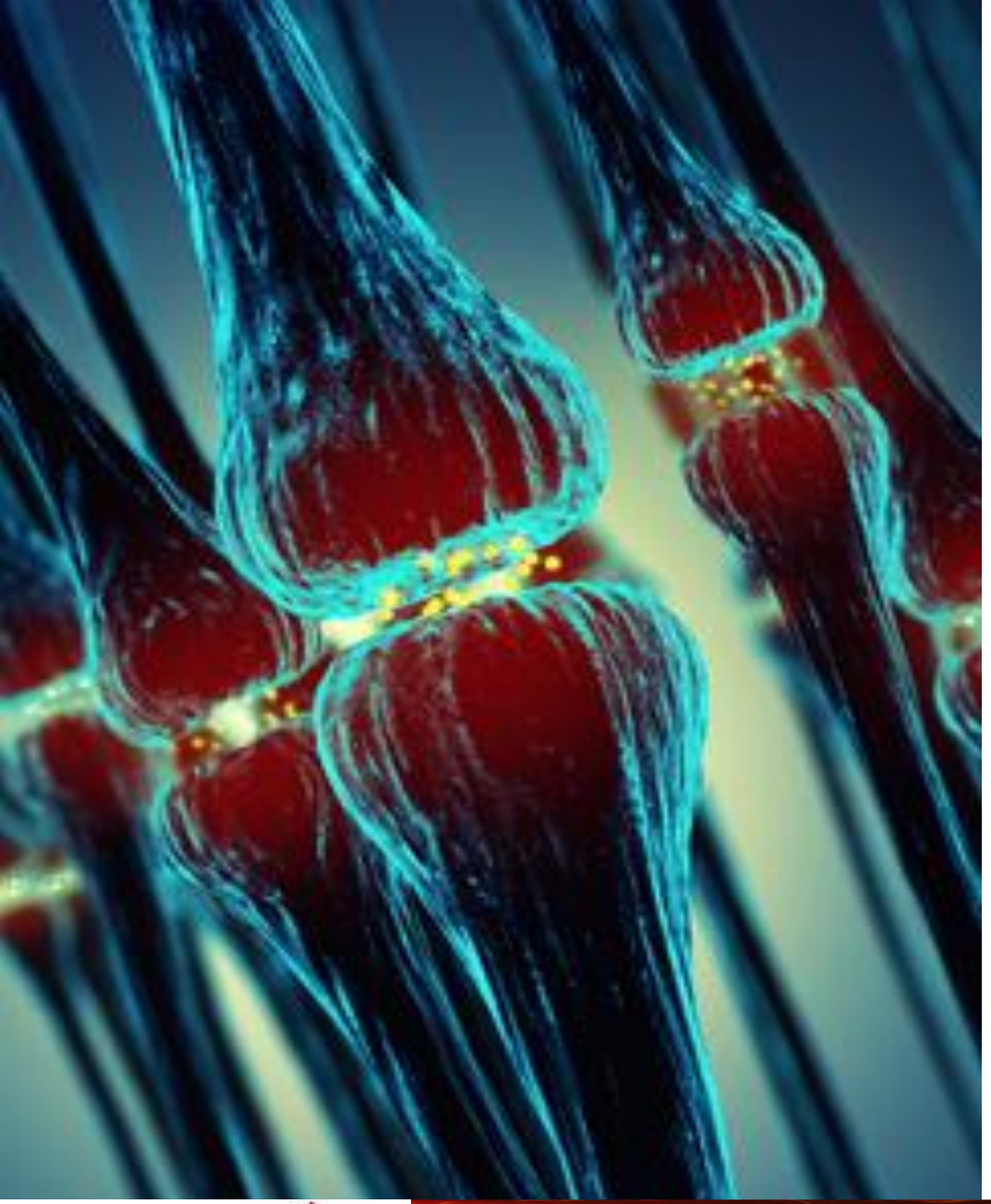
- Regulation of calcium channels
- Production of nitric oxide
- Prostacyclin formation
- Neurotransmitter production
- Glucose regulation

Omega 3 and Mitochondrial Function

Scientific literature - mitochondrial dysfunctions in molecular pathogenesis of neurodegenerative diseases
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.



L-Theanine

L-Theanine unique amino acid originally found in tea.

It is biologically active compound responsible for promoting relaxation by decreasing cortisol levels during stress and regulating neurotransmitter activity in the brain

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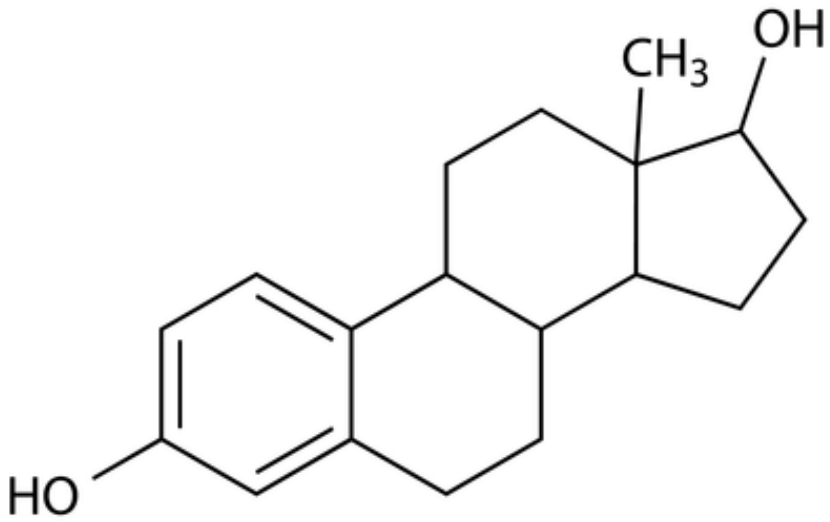
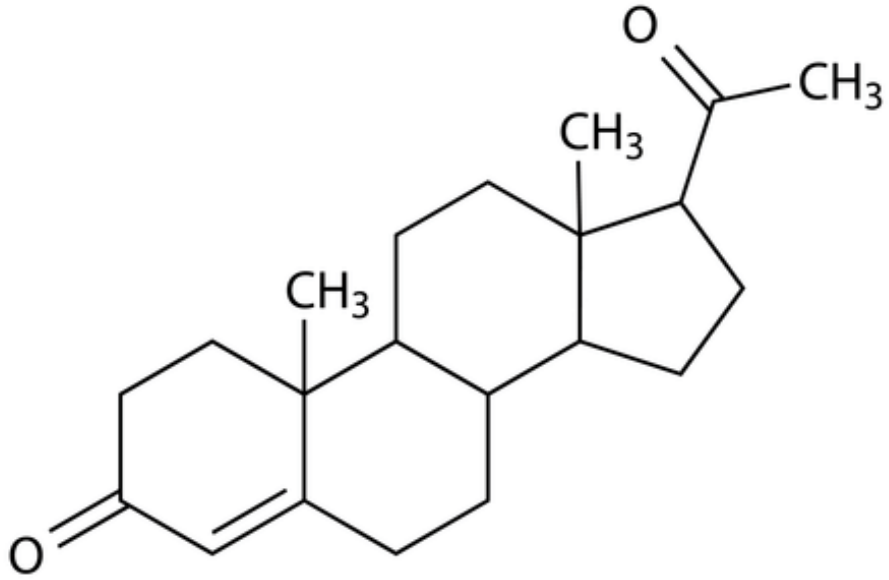
What About the Use of HRT?

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



Estradiol



Progesterone

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**

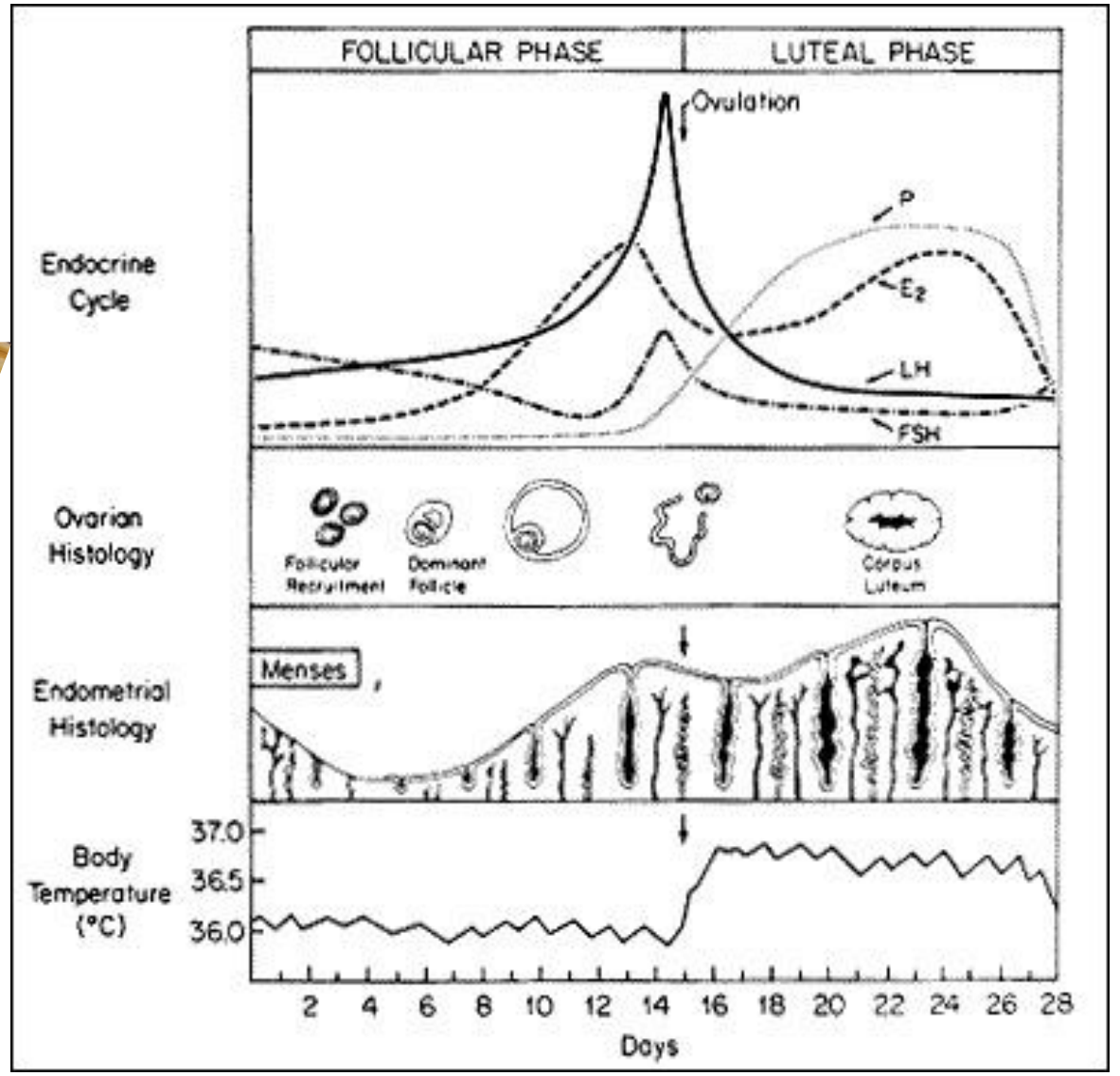
- **E2 prevents senescence in cells, such as endothelial progenitor cells and bone marrow stromal osteoblasts**

17β-E2 prevents depletion of ATP, preserves ΔΨm, 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

The Menstrual Cycle: A complex system



Carr BR, Wilson JD. Disorders of the ovary and female reproductive tract. In: Braunwald E, Isselbacher KJ, Petersdorf RG, et al, eds. Harrison's Principles of Internal Medicine. 11th ed. New York: McGraw-Hill, 1987: 1818-1837.

Nuts and Bolts of Prescribing Human Bioidentical Hormones

- Review all the available commercial options
- Review what a compounding pharmacy can do for your patients
- How to monitor and measure hormones
- Hormone level goals
- Patient goals and outcomes

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

Table 1 Recommendations for hormone therapy

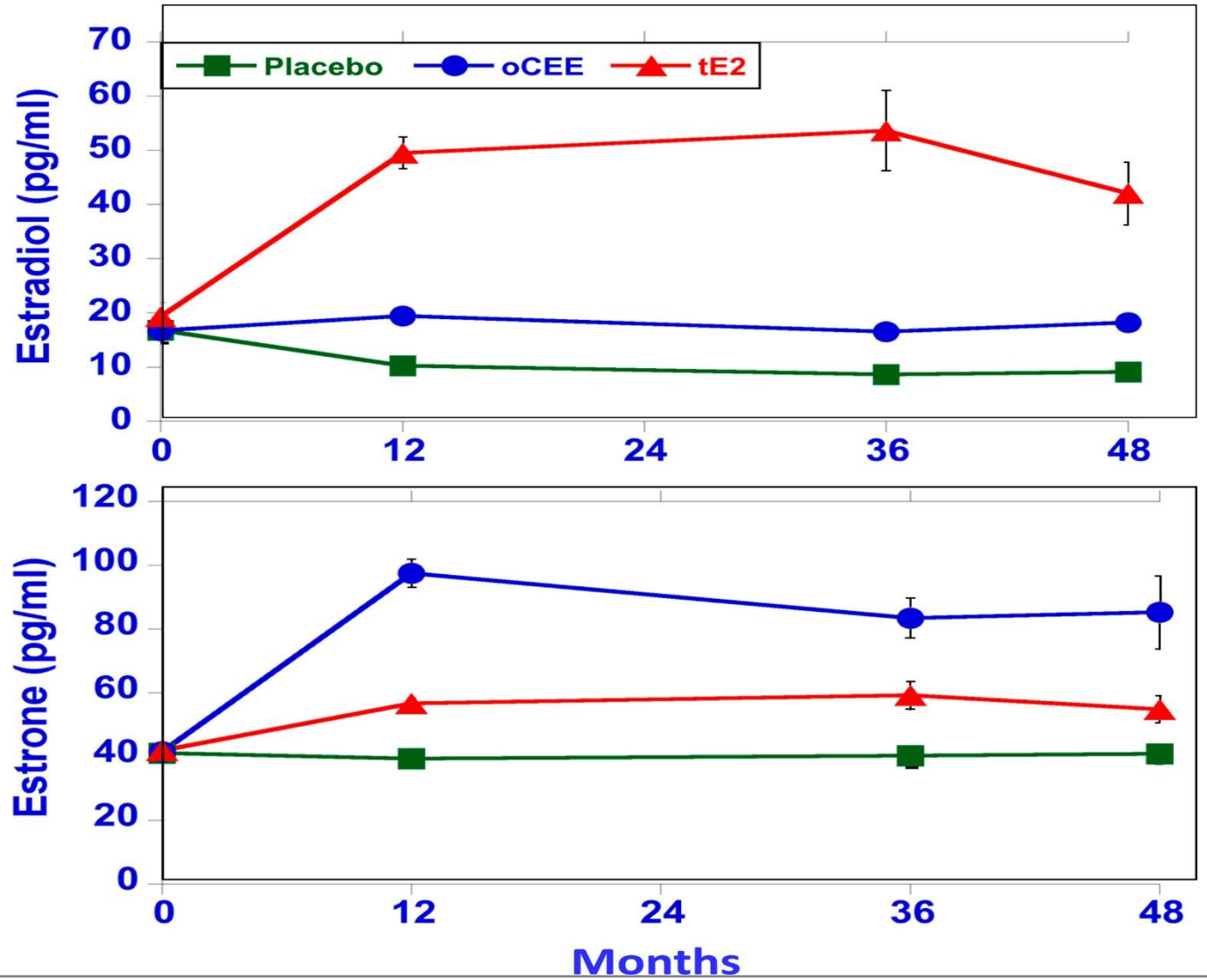
Absorption of E2 from any of the commercial products is variable
Levels should be monitored at least annually

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

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 17β-estradiol: 50 µg/day**

- **After Women's Health Initiative - recommendations were for use of "lowest" dose of estrogen product.**
- **Note: serum levels 17β-estradiol in oCEE-treated group did not exceed levels indicative of menopause required for entry into study**

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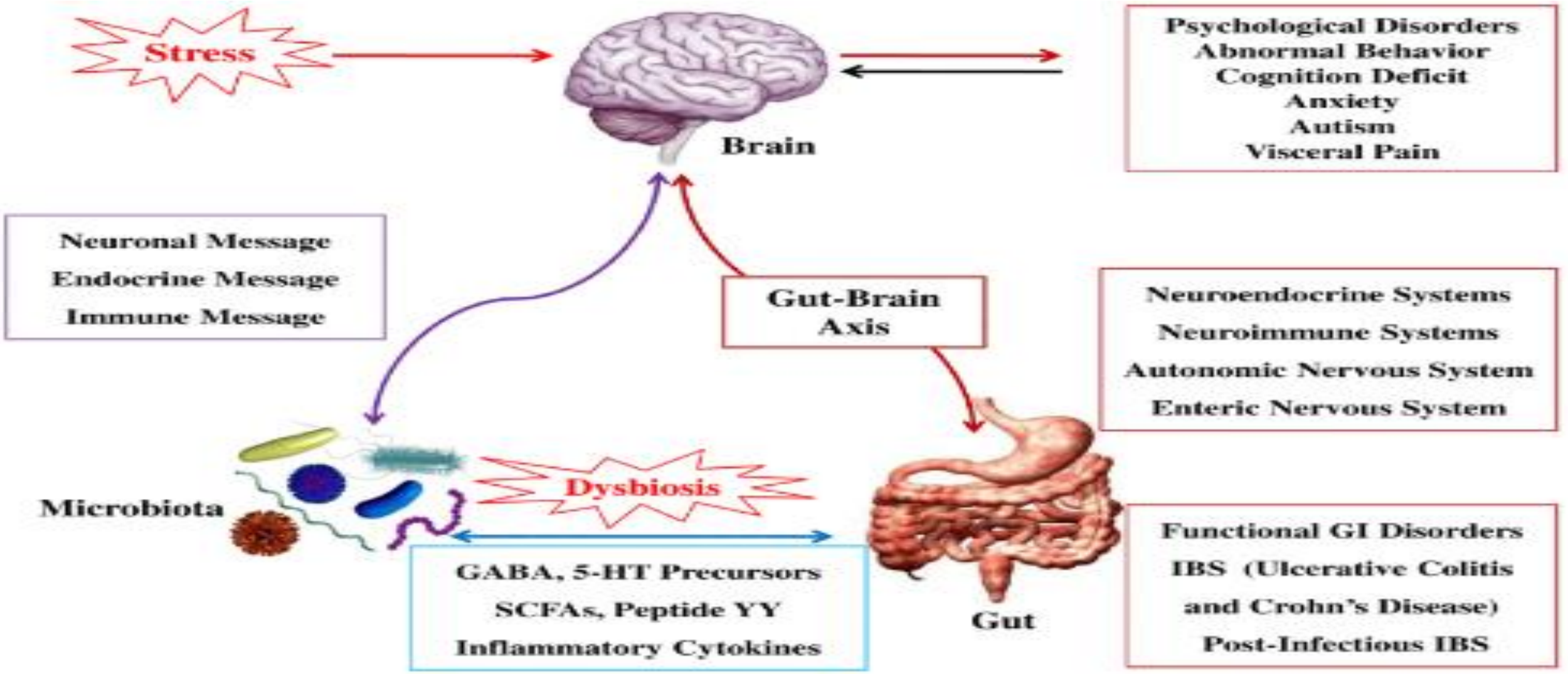
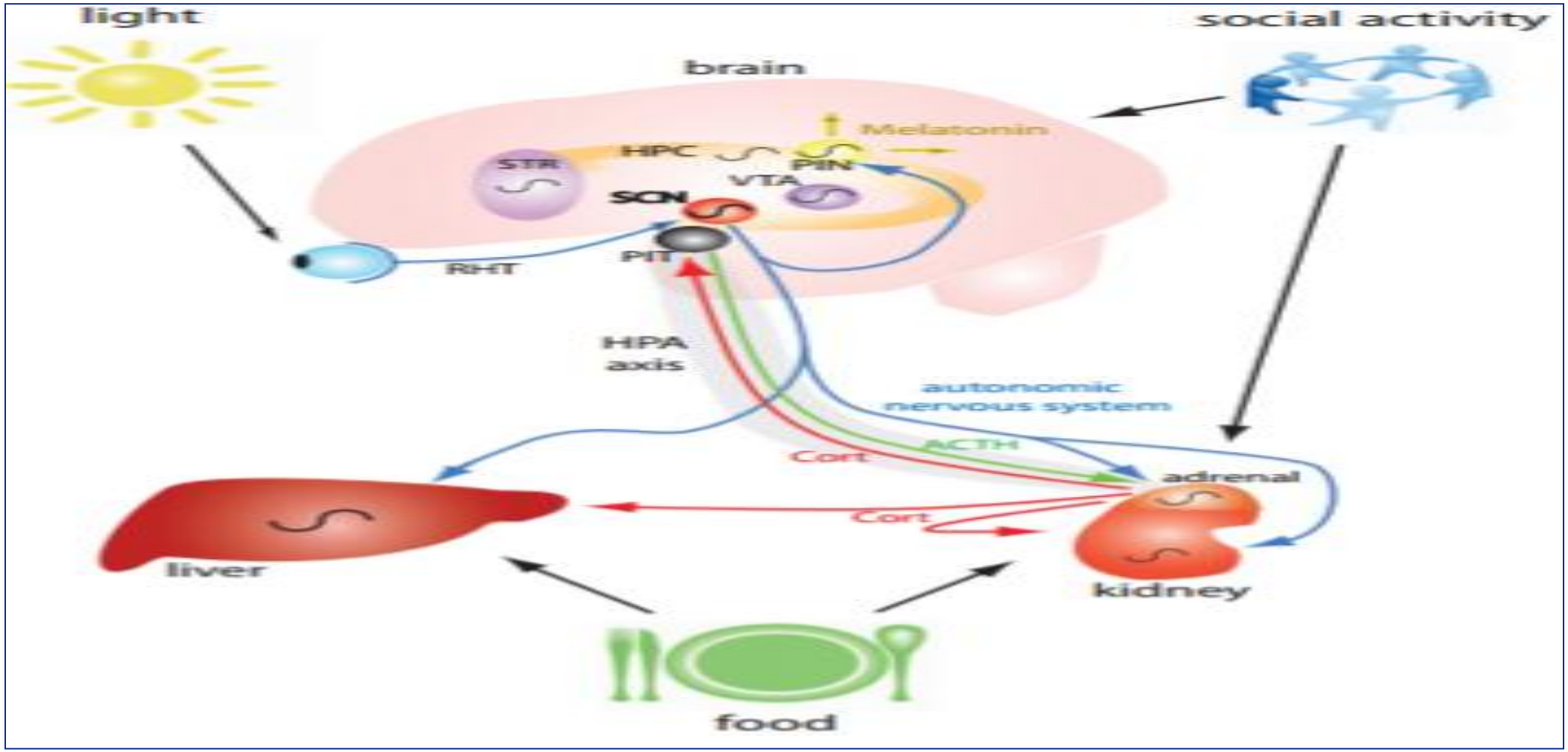
An update on hormone therapy in postmenopausal women: mini-review for the basic scientist
Virginia M. Miller and S. Mitchell Harman
American Journal of Physiology-Heart and Circulatory Physiology 2017 313:5, H1013-H1021

Putting it All Together!

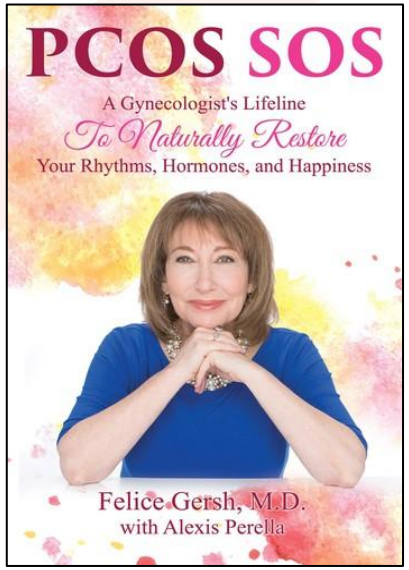


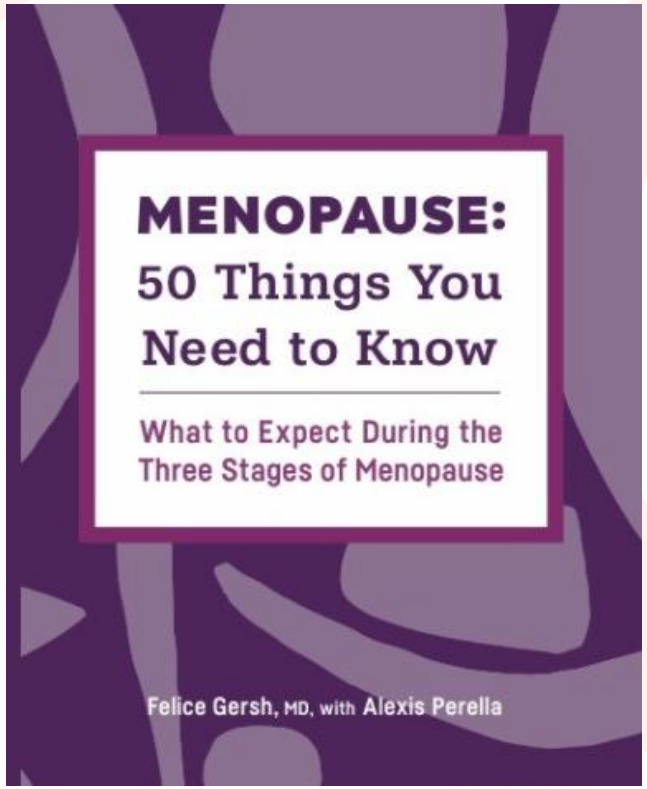
Path to Mental Health (and add in hormones!)

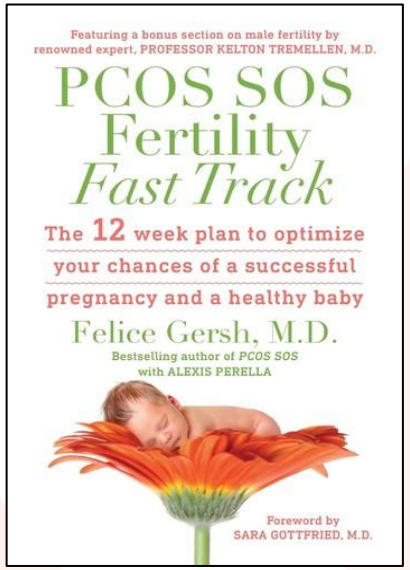


Behav Neurosci 128(3) pg 326-43, 2014.pdf

Thank *you*







Let's keep in touch!

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