

# Women, Hearts, and Hormones:

New understandings of the foundations of female cardiovascular health and the impact of menopause

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# Disclosures

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- Speaker – Cleveland HeartLab/Quest, Pure Encapsulations, L-Nutra

# Learning Objectives

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1. Understand the surprising link between reproduction and cardiometabolic health, recognizing the profound and enduring role of estrogen
2. Recognize the impact of estrogen directly and indirectly on all cardiovascular structures, and the profound implications of menopause on female cardiovascular wellbeing
3. Learn how estrogen and the Circadian Rhythm are linked and of the major role played by estrogen and the maintenance of the Master Clock
4. Learn how to implement effective strategies to help menopausal women maintain cardiovascular wellness and metabolic homeostasis, through the application of hormonal therapy, nutritional medicine, time restricted eating, stress reduction, sleep quality, and efficacious supplementation

# The significance of cardiovascular health

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Coronary artery disease (CAD) is the number one cause of death in women in the world

More than all forms of cancer, diabetes, Alzheimer's & pneumonia



# ESTROGEN

**The Major Overlooked  
Factor in Women's  
Cardiovascular Health**



# Consequences of menopause ARE the consequences of estrogen deficiency

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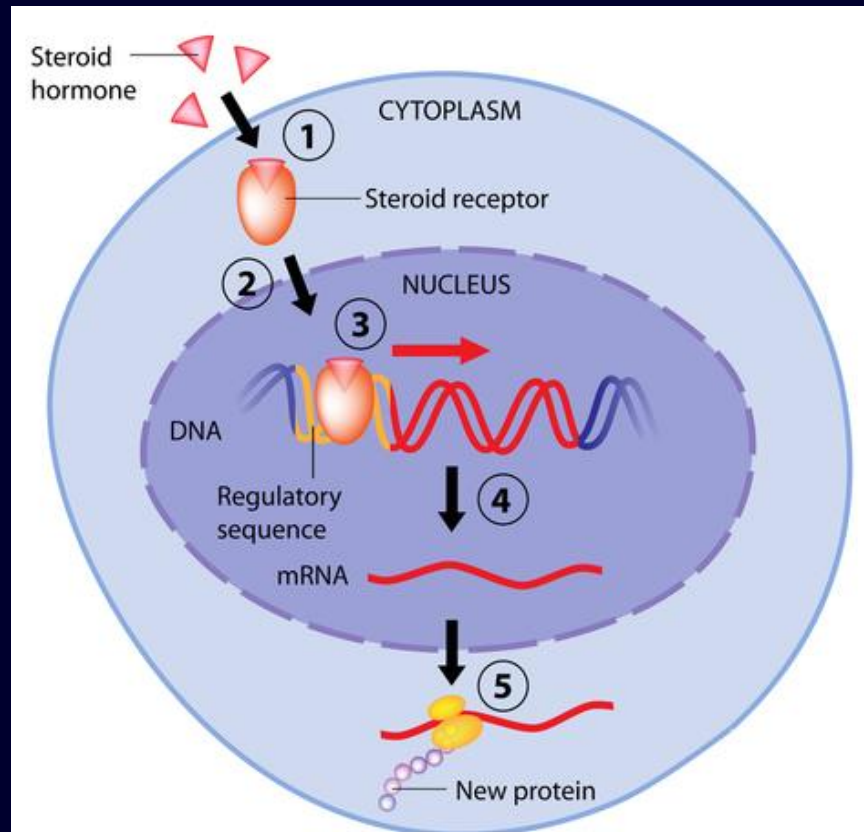
- Obesity
- Disturbed Sleep
- Mood Disorders
- Metabolic Syndrome and Diabetes
- Osteoporosis
- Cardiovascular Health and Atherosclerosis
- Alzheimer's Disease and Neuro-inflammatory
- Breast Cancer
- Fatty Liver
- GI Disorders: Colon Cancer, GERD, Malabsorption

# Menopause & cardiovascular health overview

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1. Impact on insulin resistance
2. Impact on dyslipidemia (↑LDL, oxidized LDL, ↓HDL)
3. Impact on arteries - decreased nitric oxide (↑BP) and other effects
4. Impact on the myocardium
5. Impact on gut microbiome (Estrobolome) & oral cavity - impaired gut barrier function - reduced Nitric Oxide production
6. Impact on estrogen metabolites – role of 2 MethoxyEstradiol
7. Impact on Circadian Rhythm
8. Impact on adipose tissue
9. Impact on mitochondrial function – oxidative stress

# Estrogen basics



- **ER alpha** → Regulates genes
  - Primarily expressed in the gonadal organs: uterus, ovary, prostate, testes, and breast, and in the hypothalamus of the brain, mast cells
- **ER beta** → Regulates genes
  - Primarily expressed in *non-gonadal* tissues: GI tract, colon, bone marrow, vascular endothelium, lung, bladder, B cells, and much of brain
- **Membrane-associated ER** →
  - No effect on genes, but rapid effects on cellular signaling



# Estrogen is supportive of a wide variety of physiological functions

## Estrogen receptors are everywhere!

### Estrogen receptors

1. Influence gene expression
2. Activate non-genomic pathways

Central Nervous System

Skin

Endothelium

Smooth muscle cells

Heart

Breast

Liver

Gastrointestinal Tract

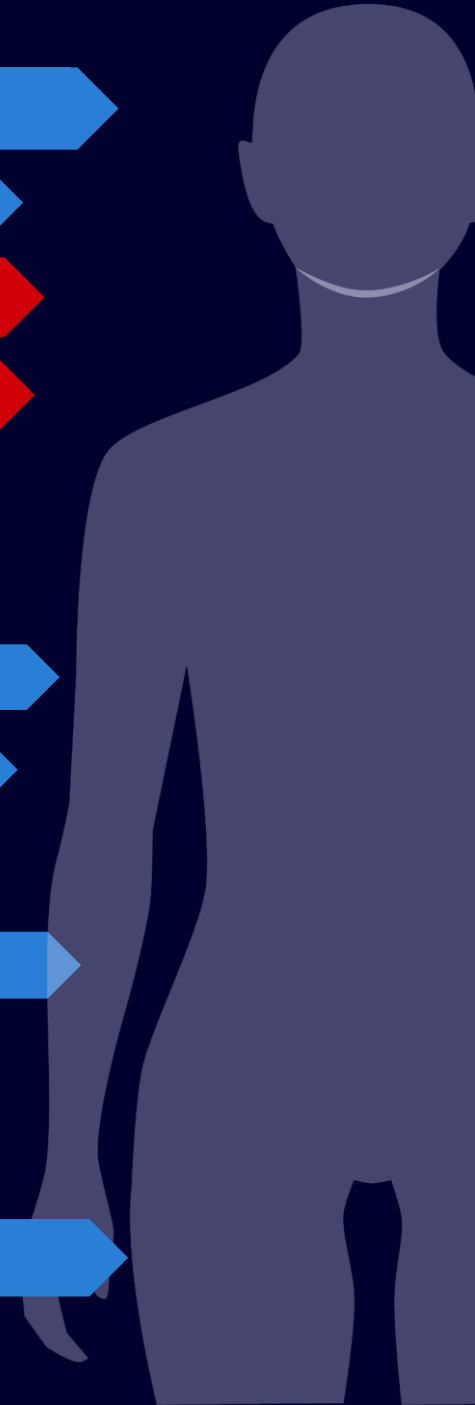
Ovary/Uterus

Bladder/Prostate

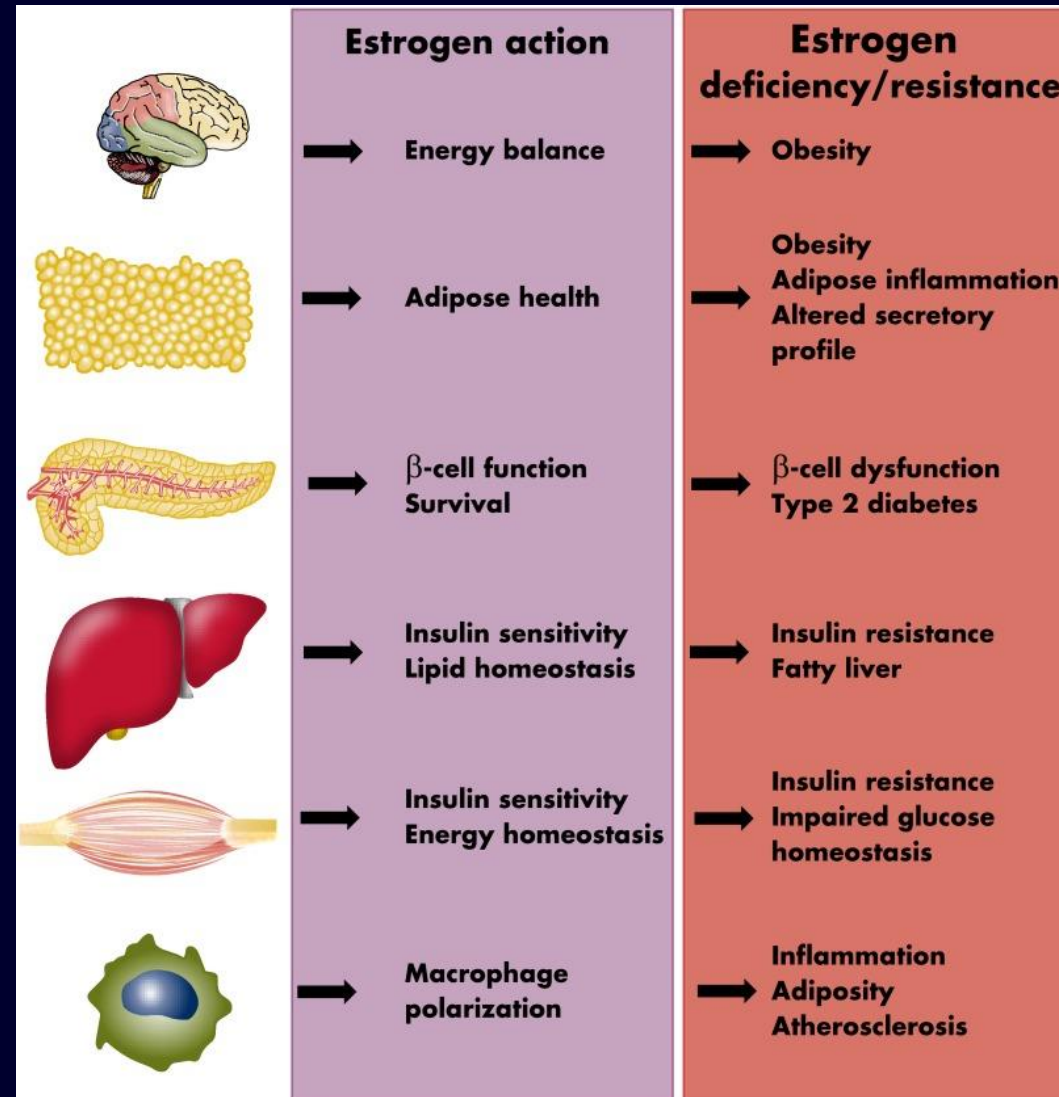
Muscles

Mitochondria

Bone/Joints/Immune Cells



# Estrogen deficiency: impact on cardio-metabolic health



Eick GN and Thronton JW. *Mol Cell Endocrinol.* 2011;334:31-38  
Mauvais-Jarvis F, et al. *Endocr Rev.* 2013; 34 (3): 309-338

# Some products of genes regulated by estrogen

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## Vasodilation and vasoconstriction

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

## Lipid Metabolism

- Lipoprotein lipase
- Apolipoproteins
- Leptin
- PON 1
- LDL receptors
- HMG-CoAR activity

## Immune activity

- Vascular-cell adhesion molecule
- Cytokines (IL1, IL6, TNF $\alpha$ )
- 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

# Estrogen Related Receptor (ERR) isoforms expressed in myocardium

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## Members of steroid hormone superfamily –

Regulate expression of genes for energy metabolism, mitochondrial biogenesis, fatty acid oxidation, oxidative phosphorylation

- ERR $\alpha$  and  $\gamma$  – share target genes in myocardium
- ERR $\beta$  – maintains proper oxygen consumption rates in myocardium

# Role of Estrogen Metabolites – 2 MethoxyEstradiol

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## Impact on cardiovascular health not via estrogen receptors

- Down regulates synthesis of Angiotensin Type 1 Receptor in liver epithelial cells
- Down regulates Endothelin 1 in coronary artery endothelial cells
- Inhibits cell growth in human aortic smooth muscle cells by decreasing ERK1/2 phosphorylation – inhibits neointima formation and smooth muscles cell growth

# Estrogen alleviates diastolic dysfunction

**Table 2** Doppler echocardiographic diastolic indices of transmitral flow in the oestradiol and placebo groups at baseline, 90 minutes, and 12 weeks

Variable	Time point	Oestradiol	Placebo	p Value
Vel E (cm/s)	Baseline (T1)	66 (19)	63 (11)	NS
	90 minutes (T2)	68 (20)	61 (13)	NS
	12 weeks (T3)	74 (22)	61 (16)	NS
Vel A (cm/s)	Baseline (T1)	81 (21)	79 (14)	NS
	90 minutes (T2)	81 (21)	76 (11)	NS
	12 weeks (T3)	75 (23)*	73 (13)*	NS
E/A ratio	Baseline (T1)	0.8 (0.2) ←	0.8 (0.1)	NS
	90 minutes (T2)	0.9 (0.2)	0.8 (0.1)	NS
	12 weeks (T3)	1.0 (0.2)†	0.8 (0.2)	0.04
DTE (ms)	Baseline (T1)	260 (42) ←	254 (22)	NS
	90 minutes (T2)	248 (40)	245 (20)	NS
	12 weeks (T3)	238 (20)*	274 (42)*	0.01
IVRT (ms)	Baseline (T1)	127 (23) ←	121 (15)	NS
	90 minutes (T2)	121 (17)	120 (16)	NS
	12 weeks (T3)	106 (16)† ←	121 (16)	0.01

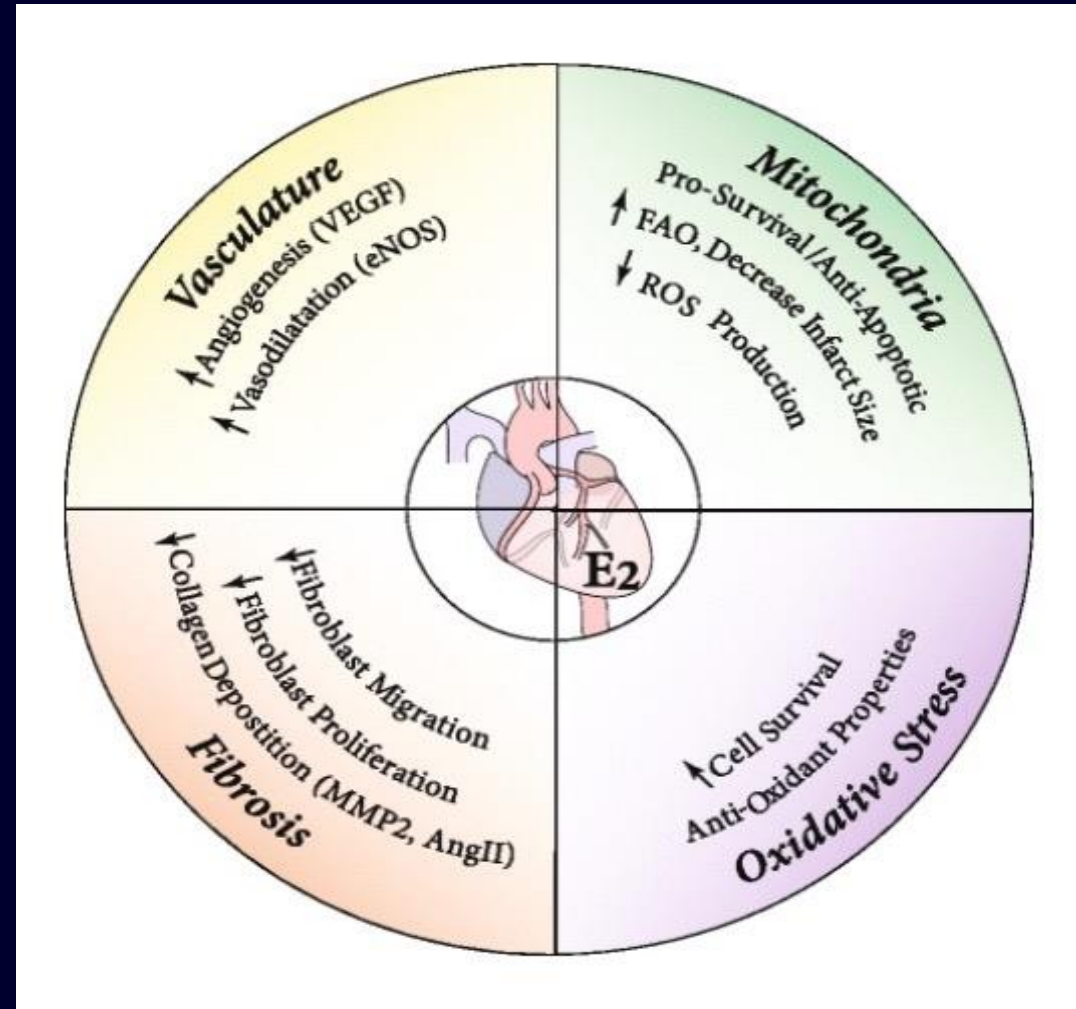
The values are expressed as mean (SD).

\*p<0.05 (T1 v T3) in the same group.

†p<0.001 (T1 v T3) in the same group.

DTE, deceleration time of mitral E wave; E/A, the ratio between the peak velocity of mitral E and A wave; IVRT, isovolumic relaxation time; Vel A, peak velocity of mitral A wave; Vel E, peak velocity of mitral E wave.

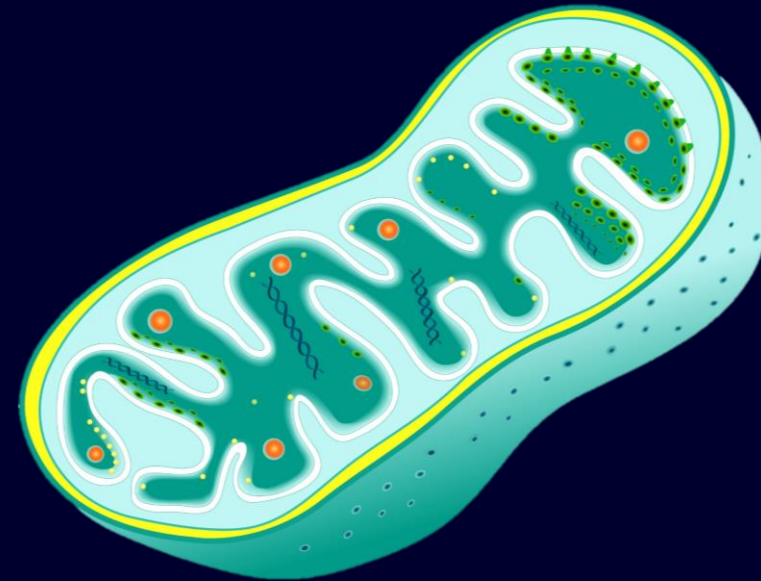
# Estrogen and the heart summary



# Estrogen supports mitochondrial health

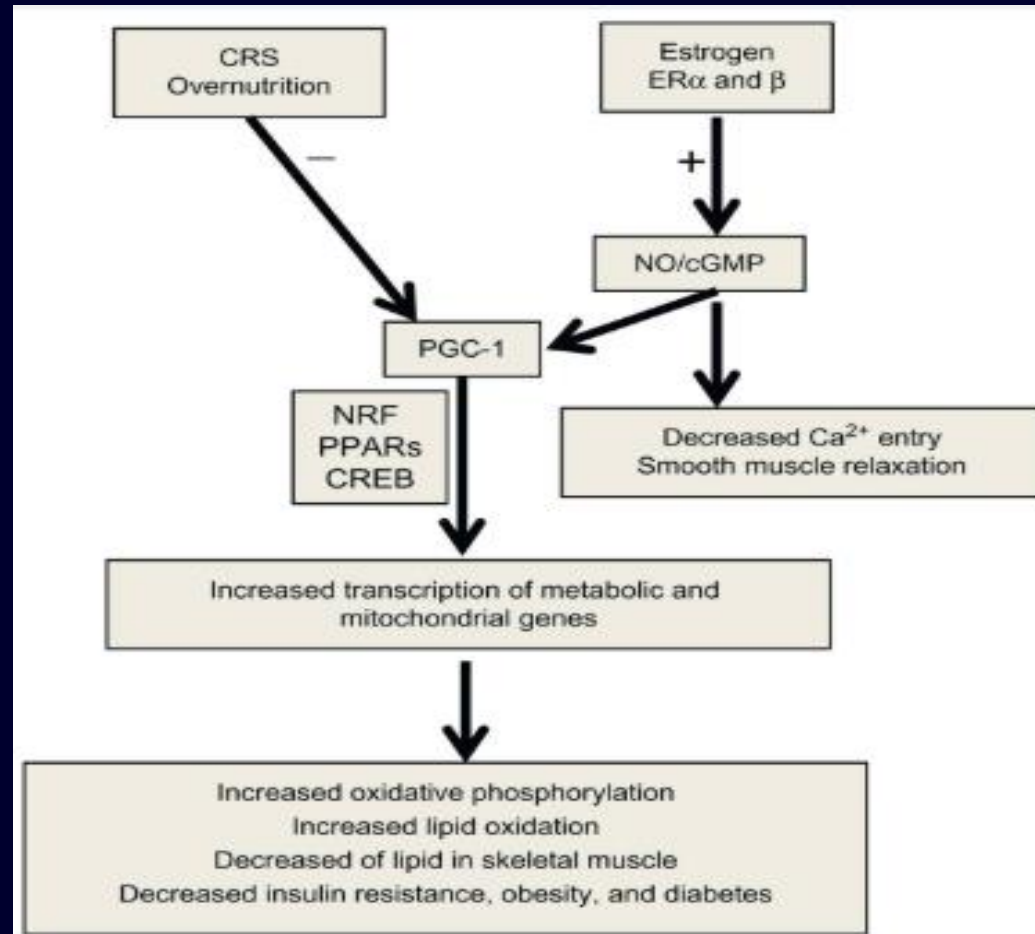
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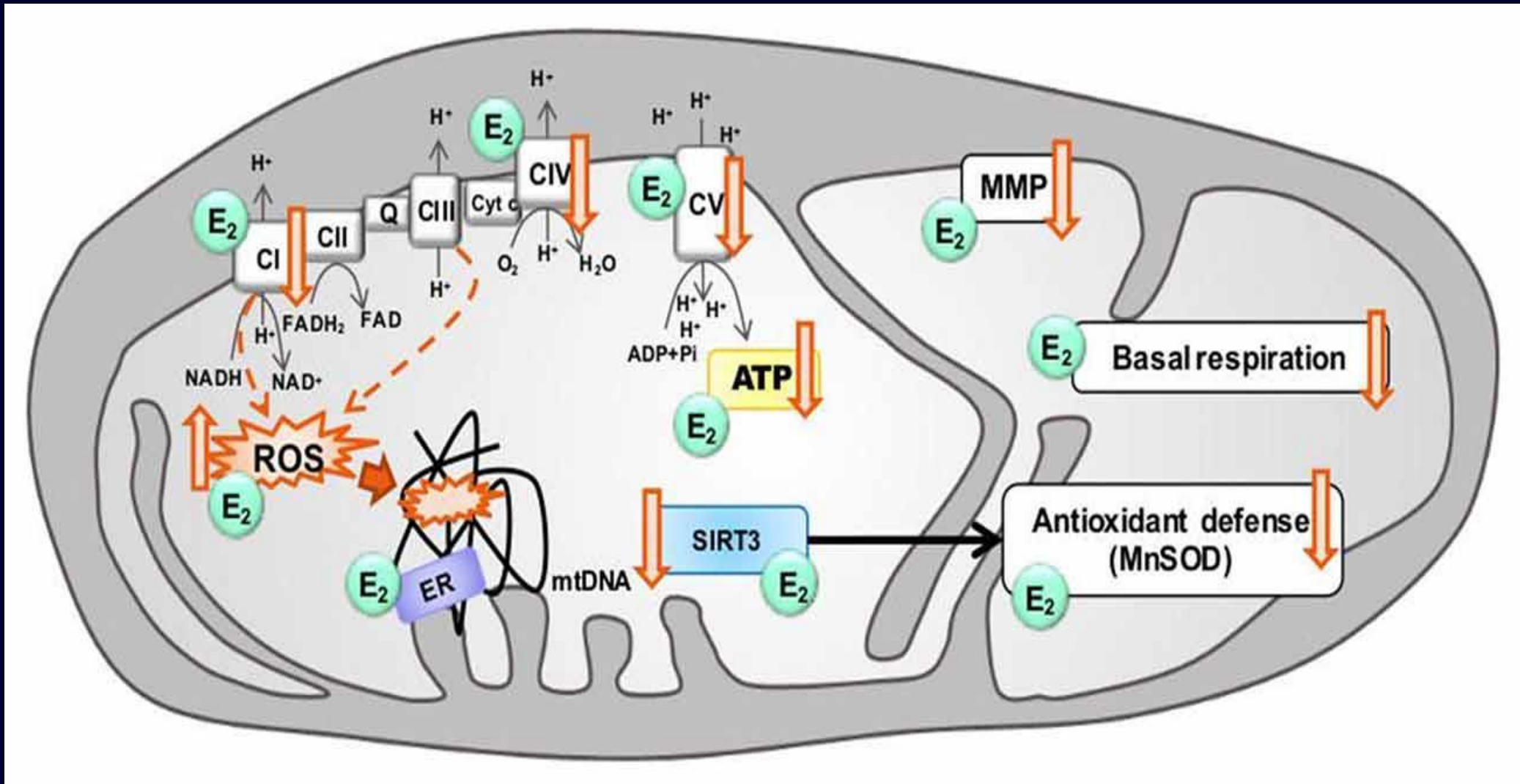
There is a growing understanding of the role which E2 plays in metabolism via its regulation of mitochondrial function





# Estrogen and mitochondrial function

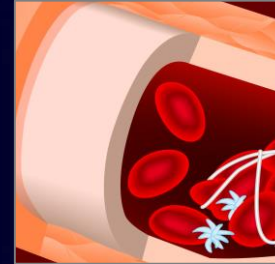




# Additional cardiovascular benefits of estradiol (E2)

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1. Insulin sensitivity & glucose metabolism



2. Lipid profile



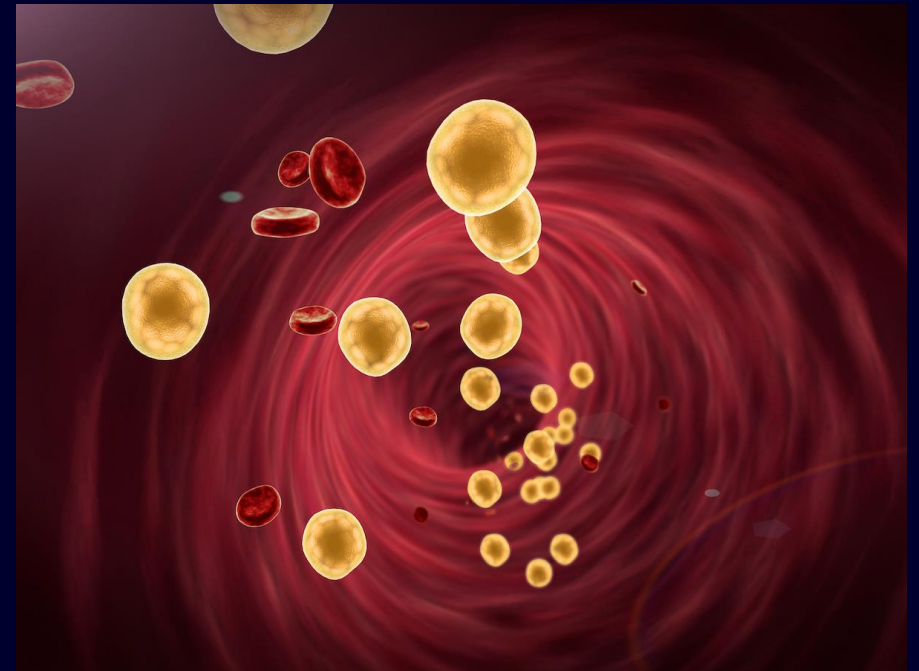
3. Endothelial function



# Estrogen supports a healthy lipid profile

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- **Supports HDL levels** by promoting apolipoprotein A-I and moderating hepatic lipase activity
- **Moderates LDL levels** by promoting levels of hepatic LDL receptors



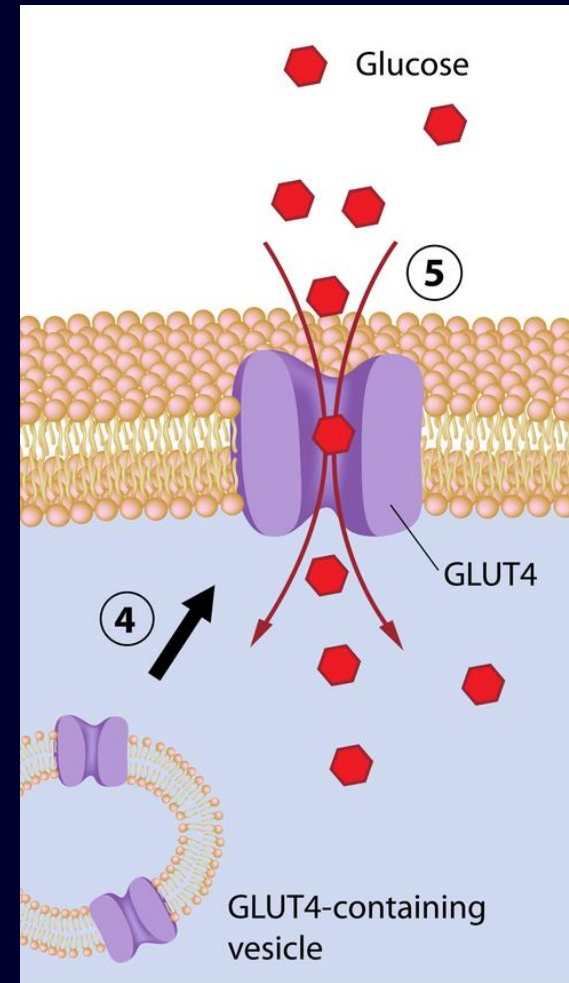
# Estrogen - lipids and paraoxonase (PON 1)

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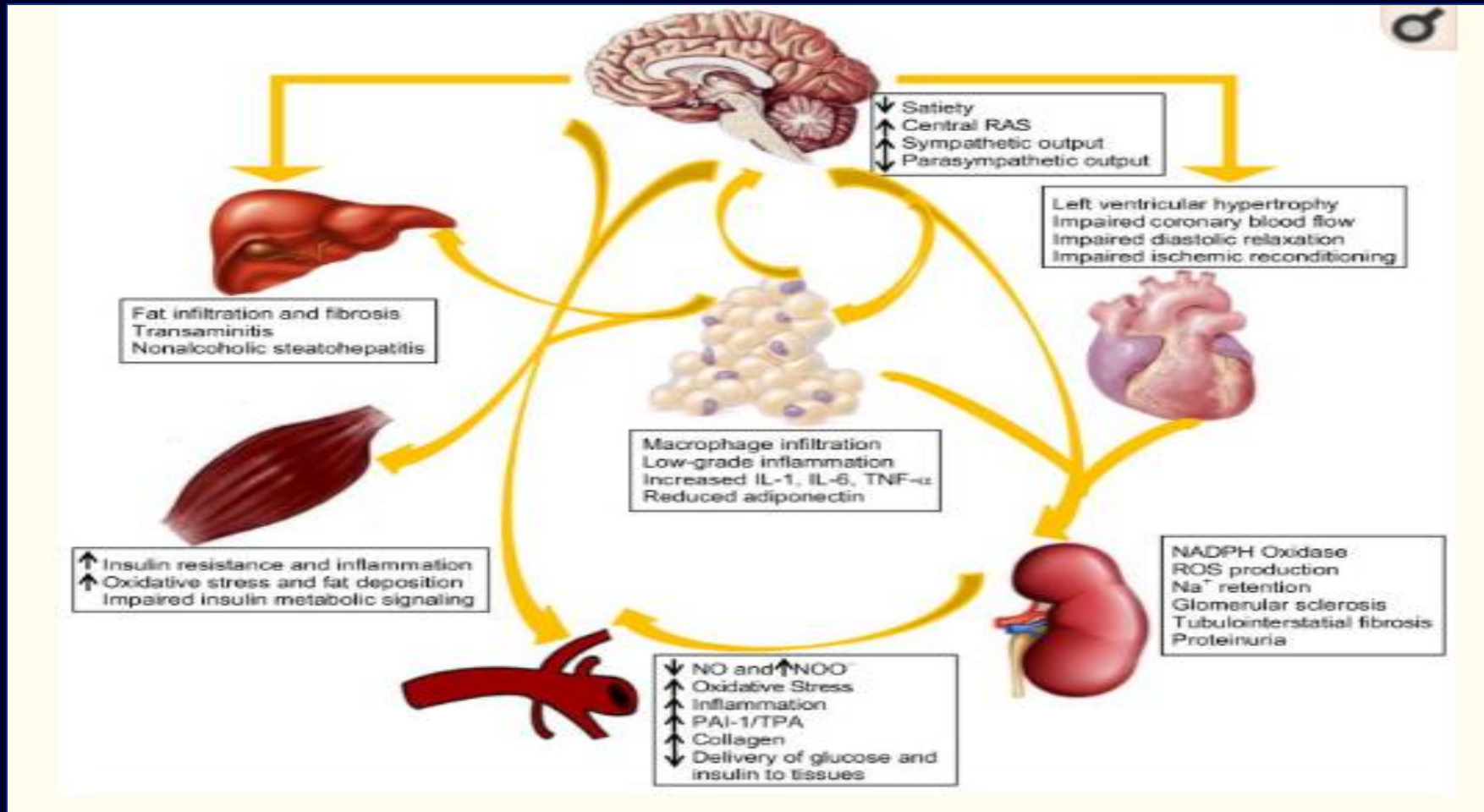
- Estrogen increases PON 1 activity & reduces oxLDL
- Oxidized low-density lipoproteins (oxLDL) involved in initiation of atherosclerosis
- PON 1 located on HDL – protects against oxidation of HDL and LDL by hydrolysing lipid peroxides
- Oxidative status reduces PON 1 activity, increases oxLDL

# Estrogen supports insulin sensitivity

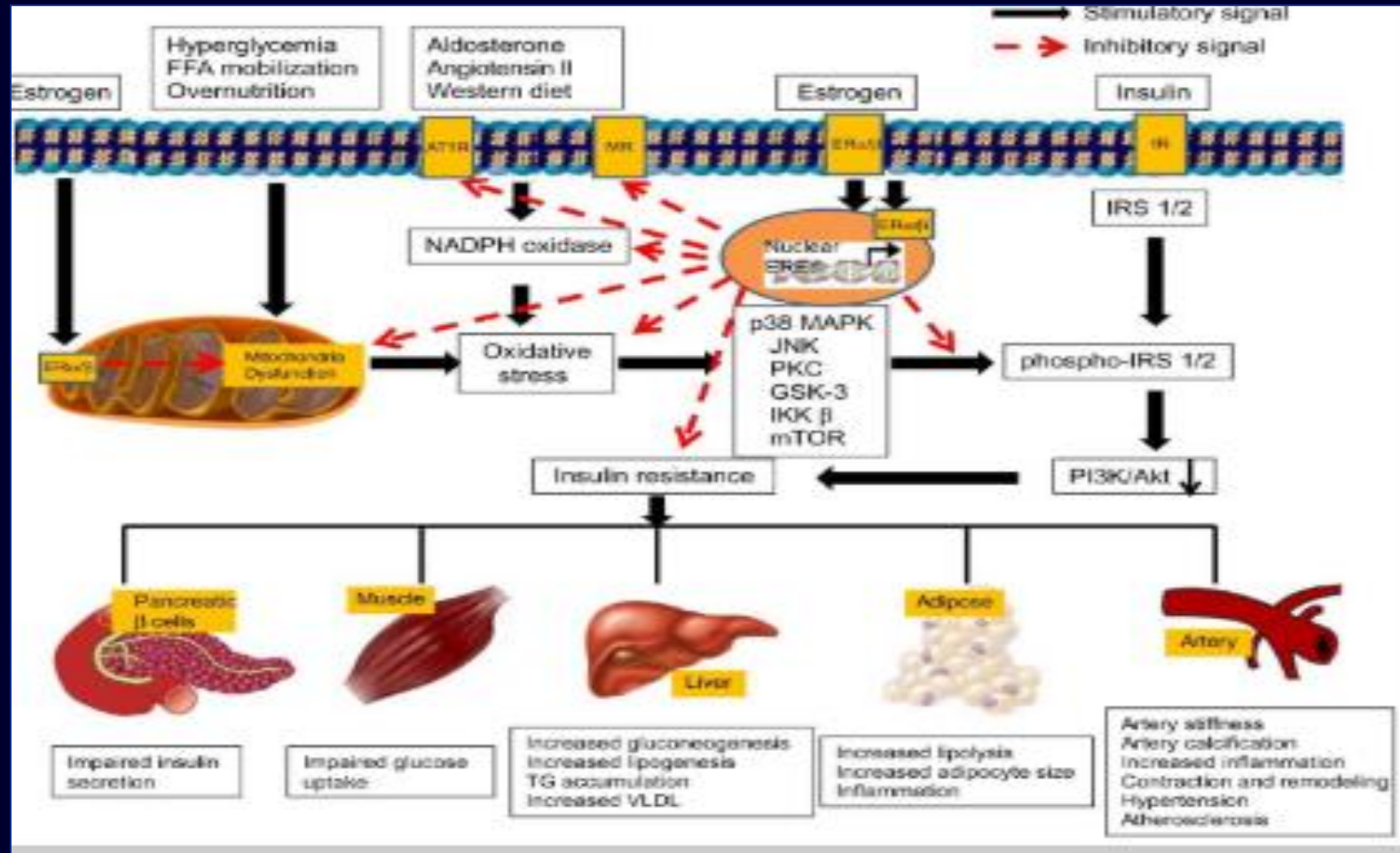
- Supports glucose transporter (GLUT3, GLUT4) function
- Enhances glucose-stimulated insulin biosynthesis
- Promotes  $\beta$  cell survival



# Menopause and the development of Cardio-Renal-Vascular-Metabolic Syndrome



# Estrogen – master of metabolic homeostasis





# The impact of menopause: insulin resistance

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- Estrogen knock-out animals consistently present with:
  - Insulin resistance
  - Hyperinsulinemia
  - Abnormal glucose homeostasis
  - Obesity
  - Hyperleptinemia

**Assess insulin sensitivity in post-menopausal patients**

...which are resolved when estradiol or ER $\alpha$  are restored

# The impact of menopause: vascular health

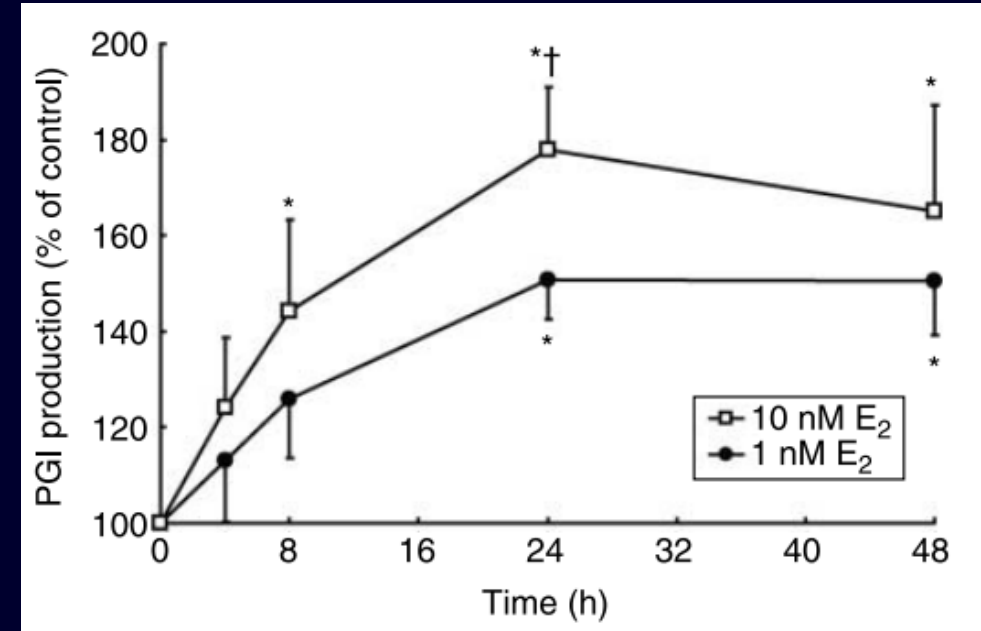
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**85% of all women in the US are hypertensive by the age of 75**

- Typically expressed as systolic hypertension
- Often develops around menopause
- Attributed to the decline in estrogen
- Risk factor for CAD and other cardiometabolic events

# Estradiol promotes prostacyclin expression

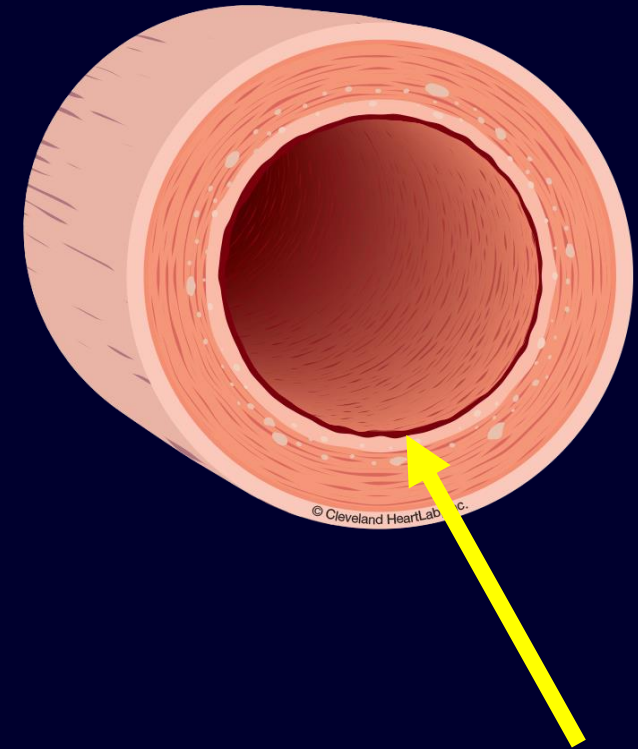
- **Prostacyclin (PGI<sub>2</sub>)**, produced by endothelial and vascular smooth muscle cells
  - Major anti-atherogenic prostanoid
  - Counter effects thromboxane – important balance in cardiovascular homeostasis
- **Estradiol**
  - E<sub>2</sub> promotes vasodilation through release of prostanoids (and others)
  - Binds to ER $\alpha$  to up-regulate cyclooxygenases, PGI Synthase, and PGI expression



Endothelial cells treated with estrogen induces PGI production in a dose dependent manner

# Introduction to the endothelium

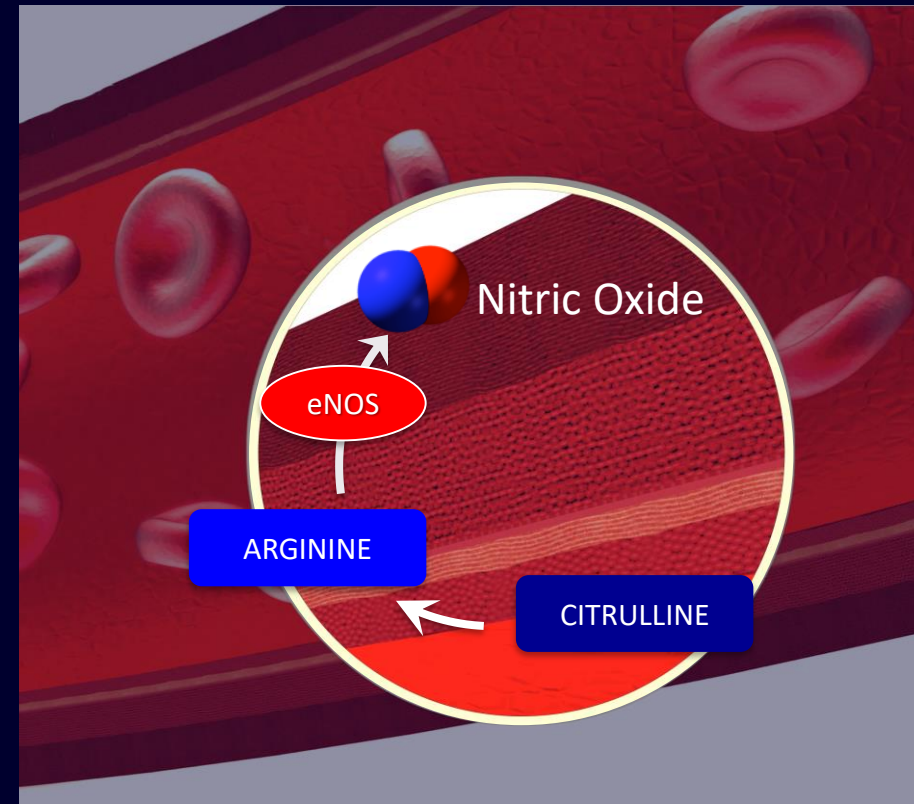
- **Simple squamous layer** (one cell thick) that lines inner surface of all blood vessels – from the heart to the smallest capillary
  - *Enough to cover the surface of 8 tennis courts*
- **Interface: circulating blood and vascular wall**
- **Classically thought of as an inert membrane**, but is now known to play an integral role in metabolic, immunologic, and CV health
- **Healthy endothelium prevents:**
  - Platelet aggregation and leukocyte adhesion
- **And controls:**
  - Vascular tone – BP, arterial stiffness, inflammation, permeability, growth, blood fluidity, and coagulation



# Estrogen supports blood pressure & endothelial function

## Estrogen supports Nitric Oxide (NO)

- **NO is a short-lived (3-5 sec half-life), lipid/water soluble gas**
- **NO supports:**
  - Healthy blood pressure
  - Reduced platelet aggregation
  - Endothelial function
  - Myocardial function



# Nitric oxide maintains endothelial health and is cardio-protective

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 **Nitric  
Oxide**

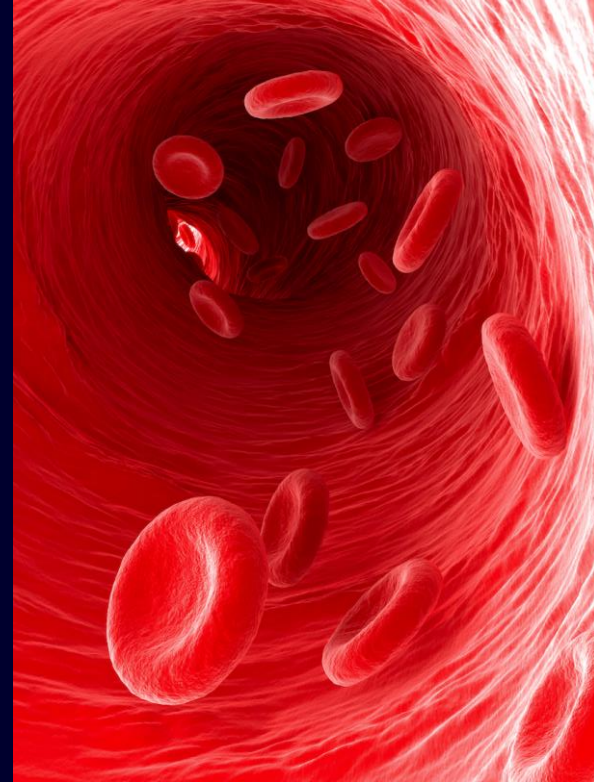
- Improve dilation of blood vessels
- Reduce blood clotting
- Reduce inflammation in artery wall
- Reduce free radical formation
- Reduce LDL oxidation
- Reduce artery wall thickening



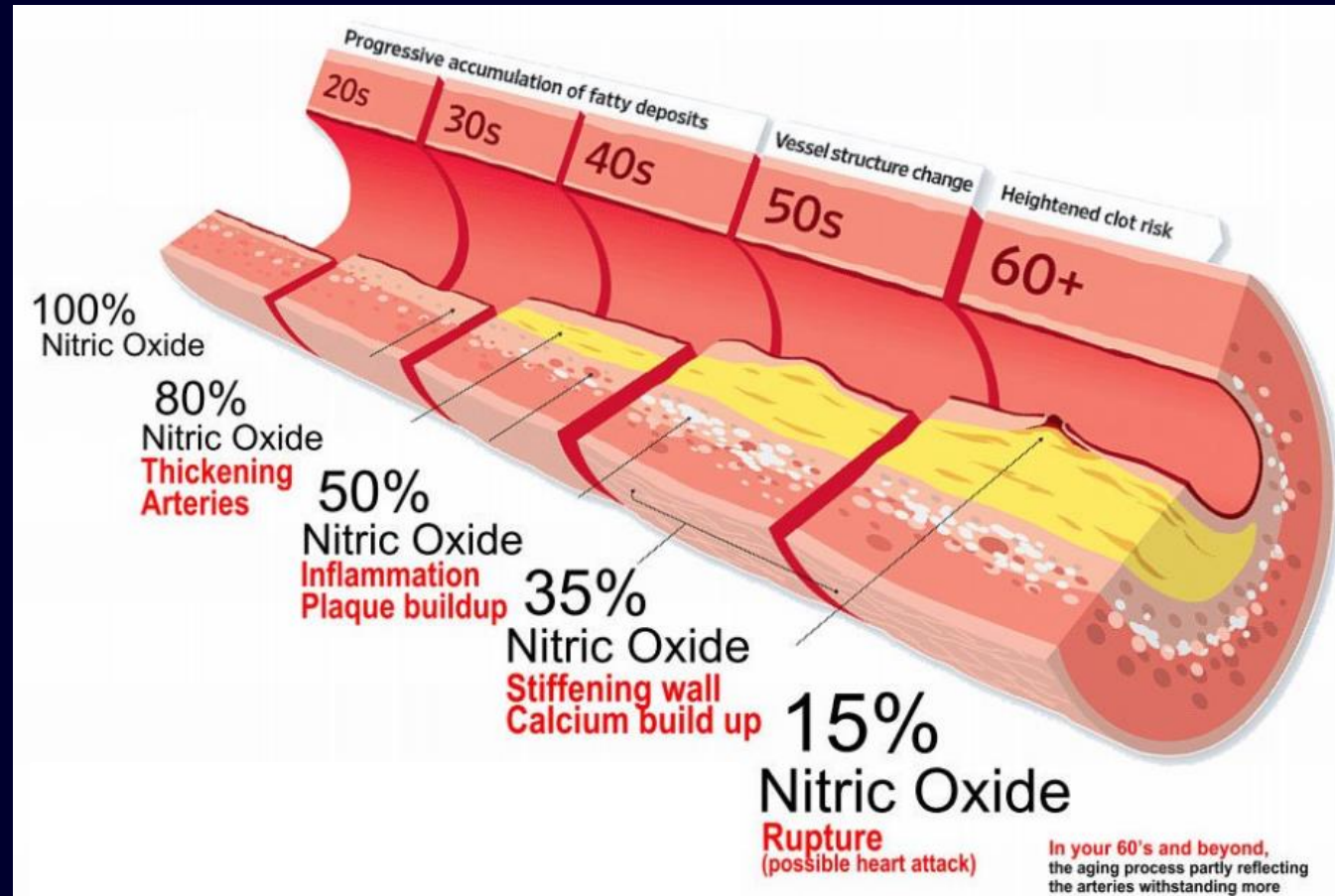
# Consequences of diminished nitric oxide

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- Endothelial dysfunction
- Platelet aggregation
- Hypertension
- Vascular dysfunction
- Thrombosis
- Cognitive decline
- Immune Dysfunction
- Chronic Inflammation
- Sexual Dysfunction (male and female)



# Progression with age: a NO perspective



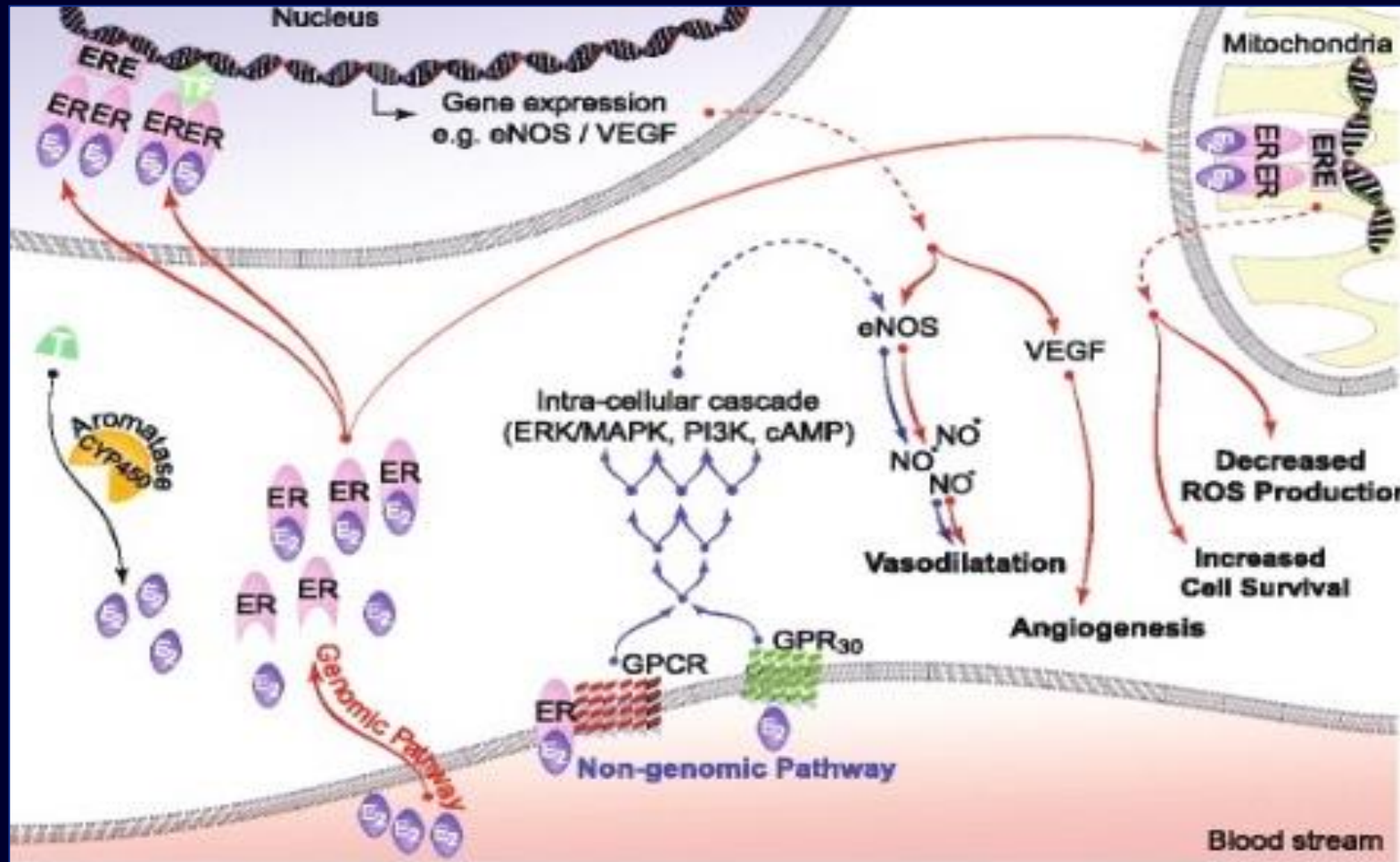
Adapted from:

Celermajer DS et al. *J Am Coll Cardiol*. 1994; 24 (2):471-476

Egashira K et al. *Circulation*. 1993; 88 (1):77-81



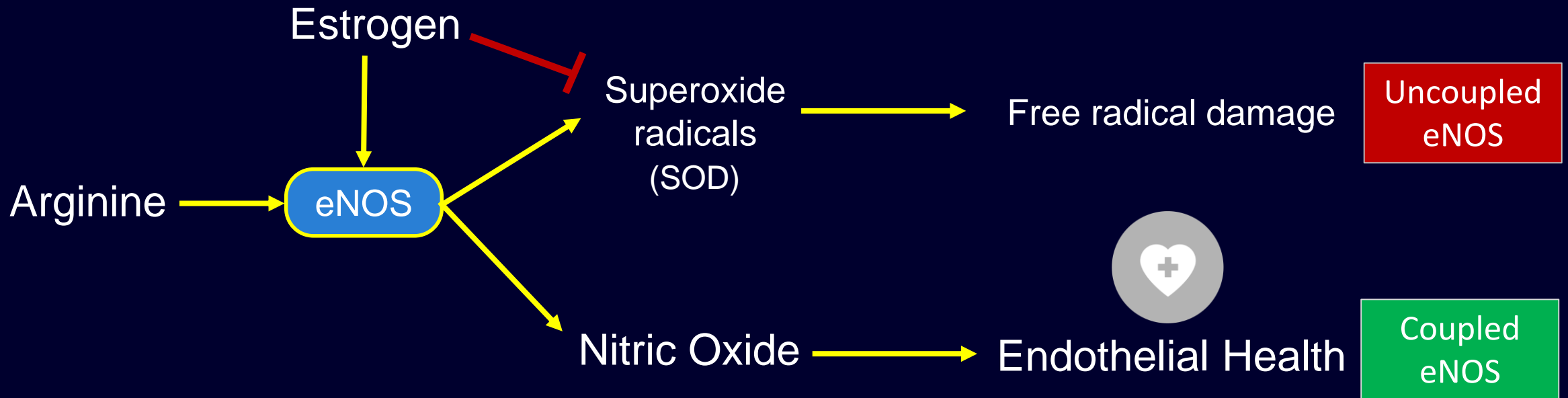
# Overview: estrogen and arterial health



# Estrogen supports nitric oxide synthesis

Estrogen supports the expression and activation of eNOS

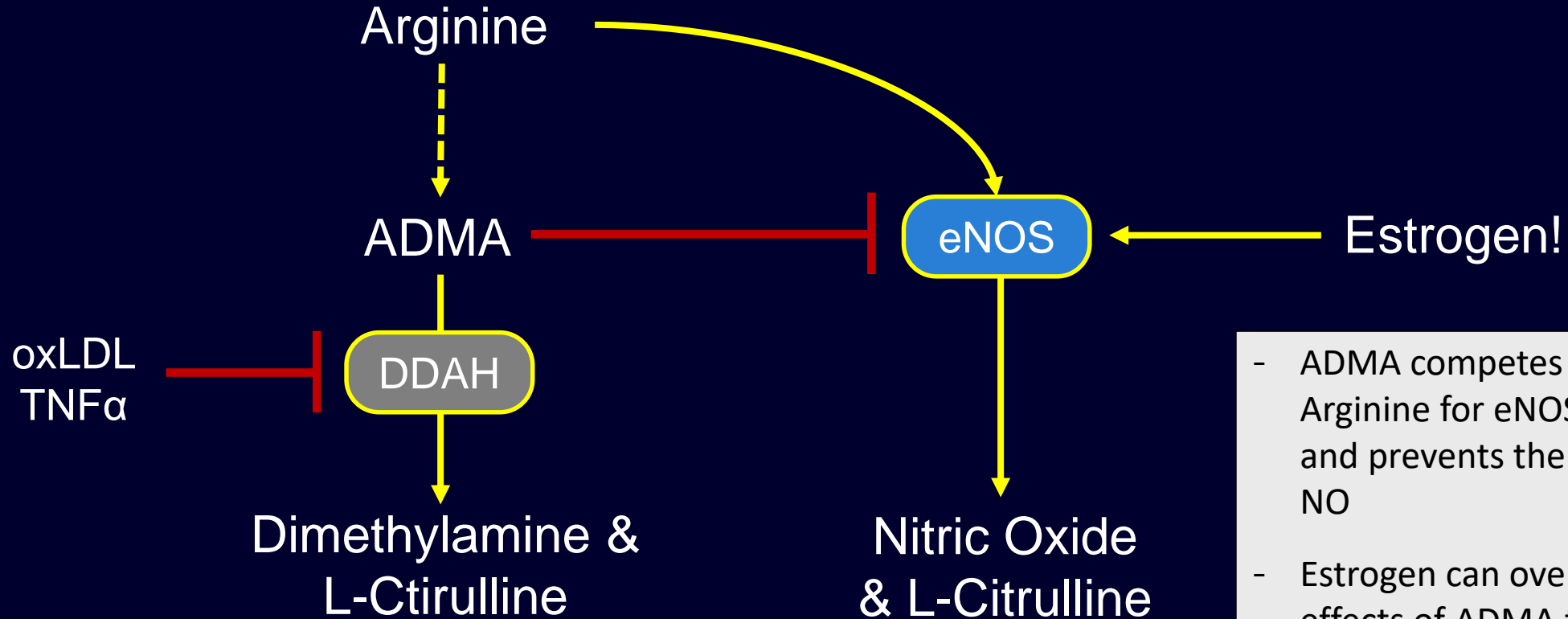
Estrogen moderates the formation of uncoupled eNOS



## SOD, Super oxide dismutase

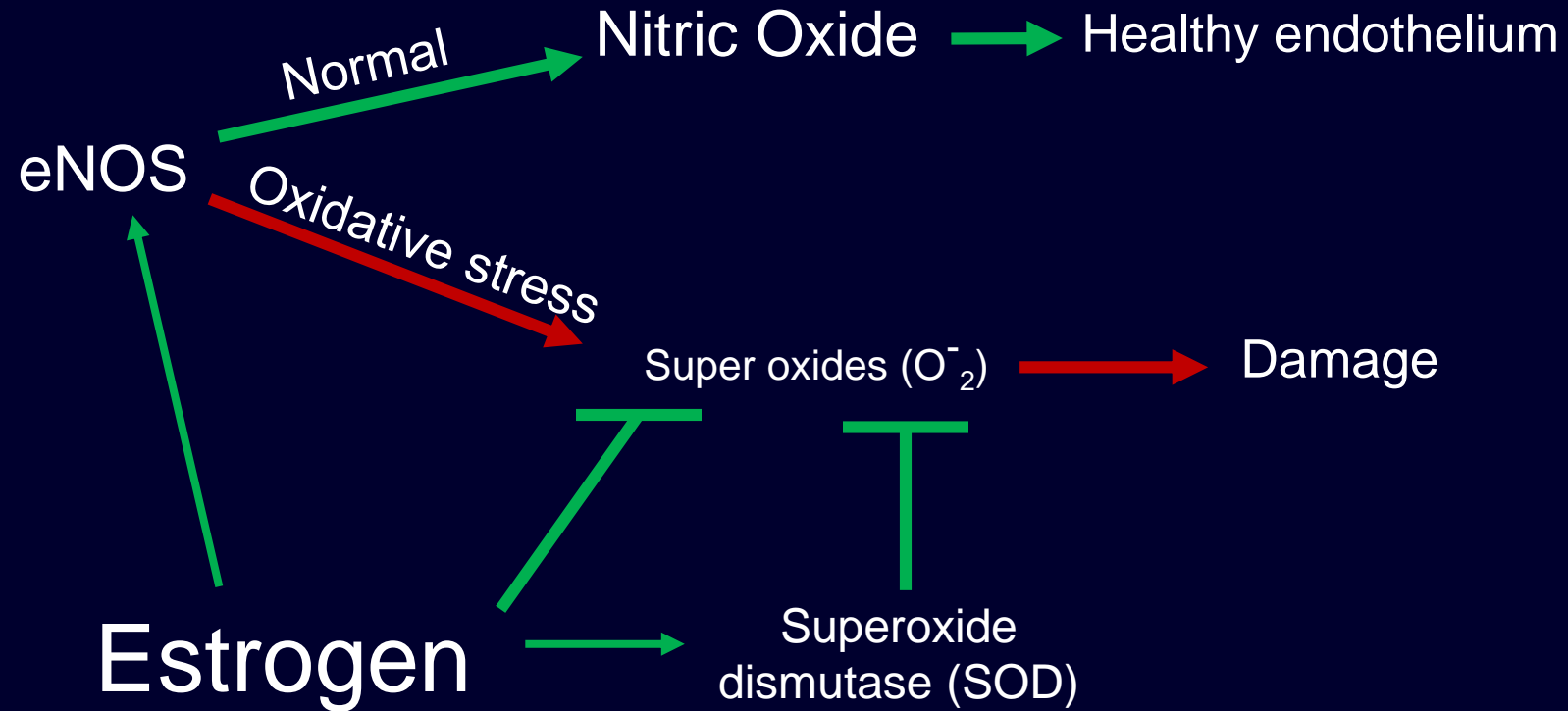
Chakrabarti S, et al. *IUBMB Life*. 2008; 606(6): 376-382  
Nevzati E et al. *Acta Neurochir Suppl*. 2015;120:141-5.  
Zhao Z et al.. *Am J Physiol Heart Circ Physiol*. 2013; 306:

# Estrogen supports nitric oxide in the presence of inflammation



- ADMA competes with Arginine for eNOS receptor and prevents the synthesis of NO
- Estrogen can overcome the effects of ADMA to increase NO production

# Estrogen: Antioxidant Activity



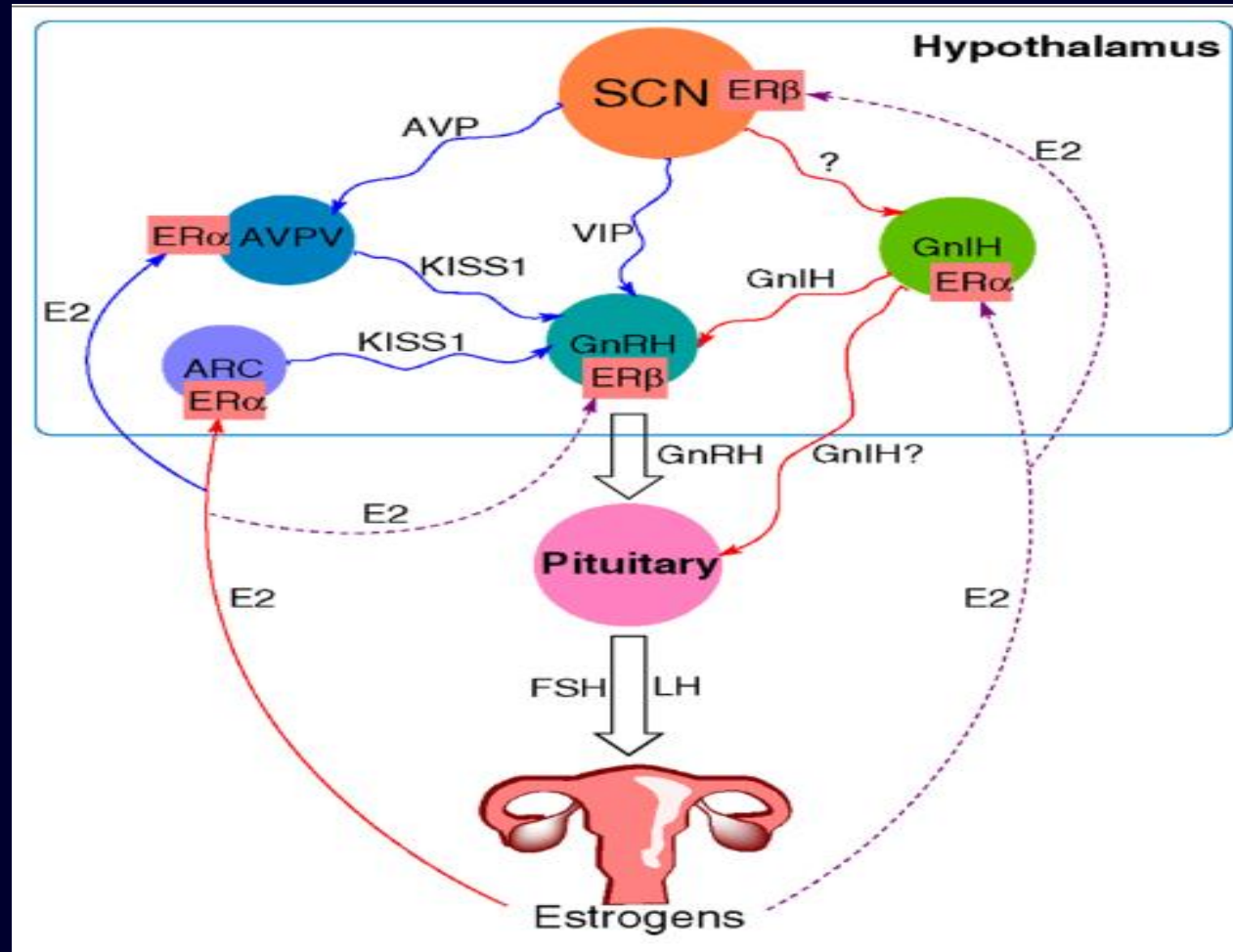
# Circadian Rhythms

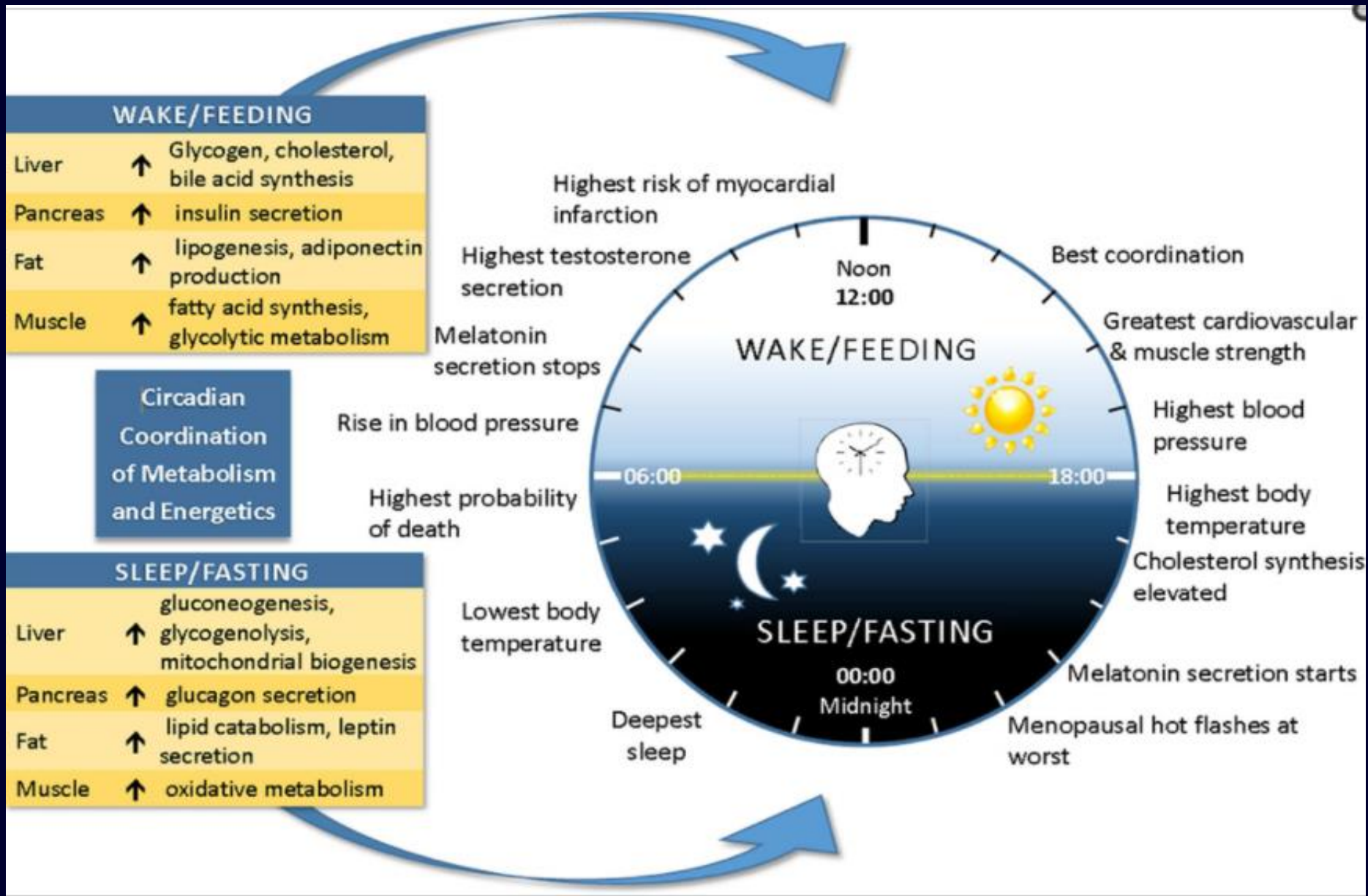
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- ~24h oscillations in physiology and metabolism that allow organisms to predict the availability of food and light.
- Estrogen is the master hormone regulating the Circadian Rhythm



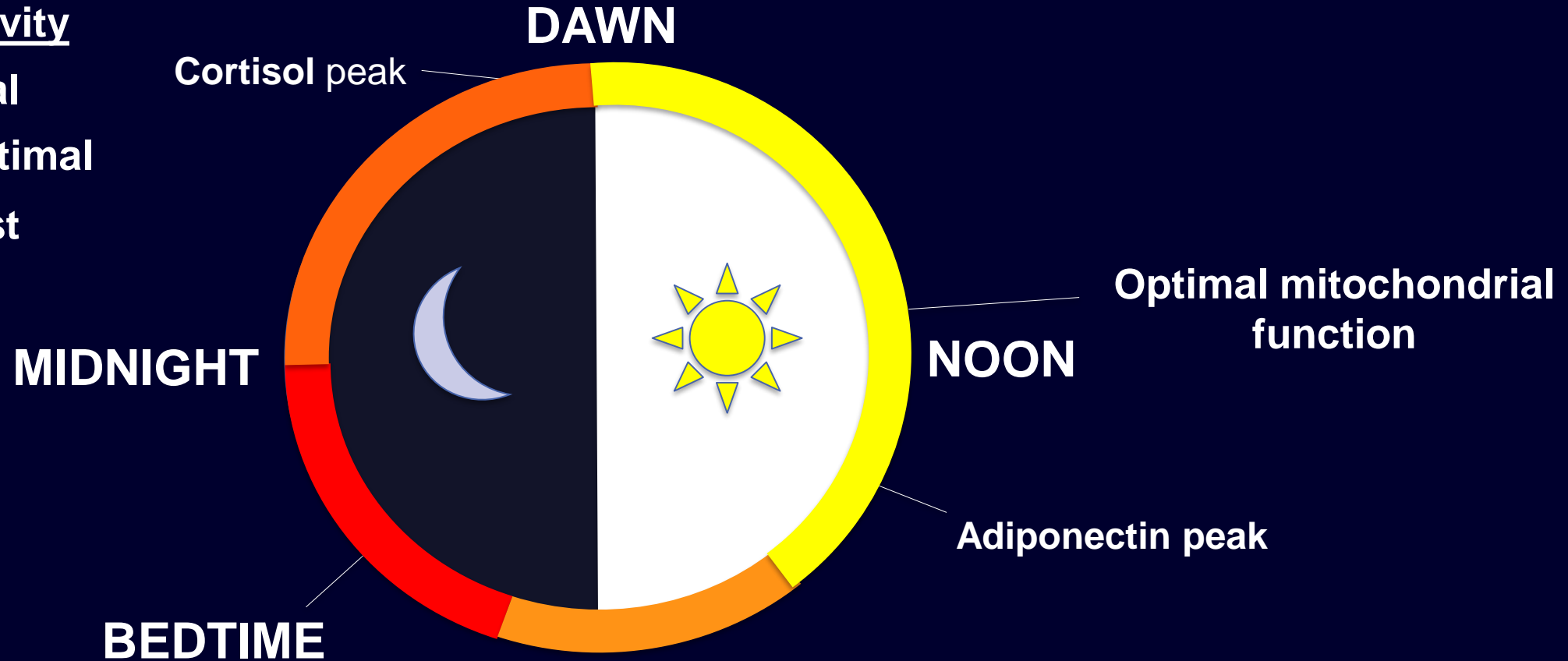
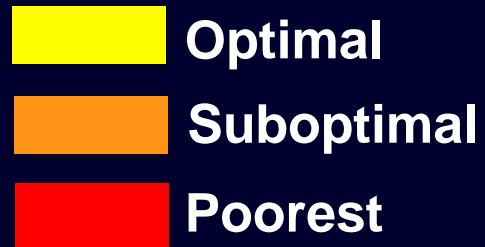
# Estrogen, reproduction, metabolism: interconnected with the circadian rhythm





# The rhythm of insulin sensitivity

## Insulin sensitivity





# Circadian disruptors

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- Nocturnal light exposure
- Improper meal timing
- Poor or interrupted sleep
- Stress
- Traveling across time zones
- Social jet lag
- Shift work
- Endocrine Disruptors



- **Loss of estrogen in women**

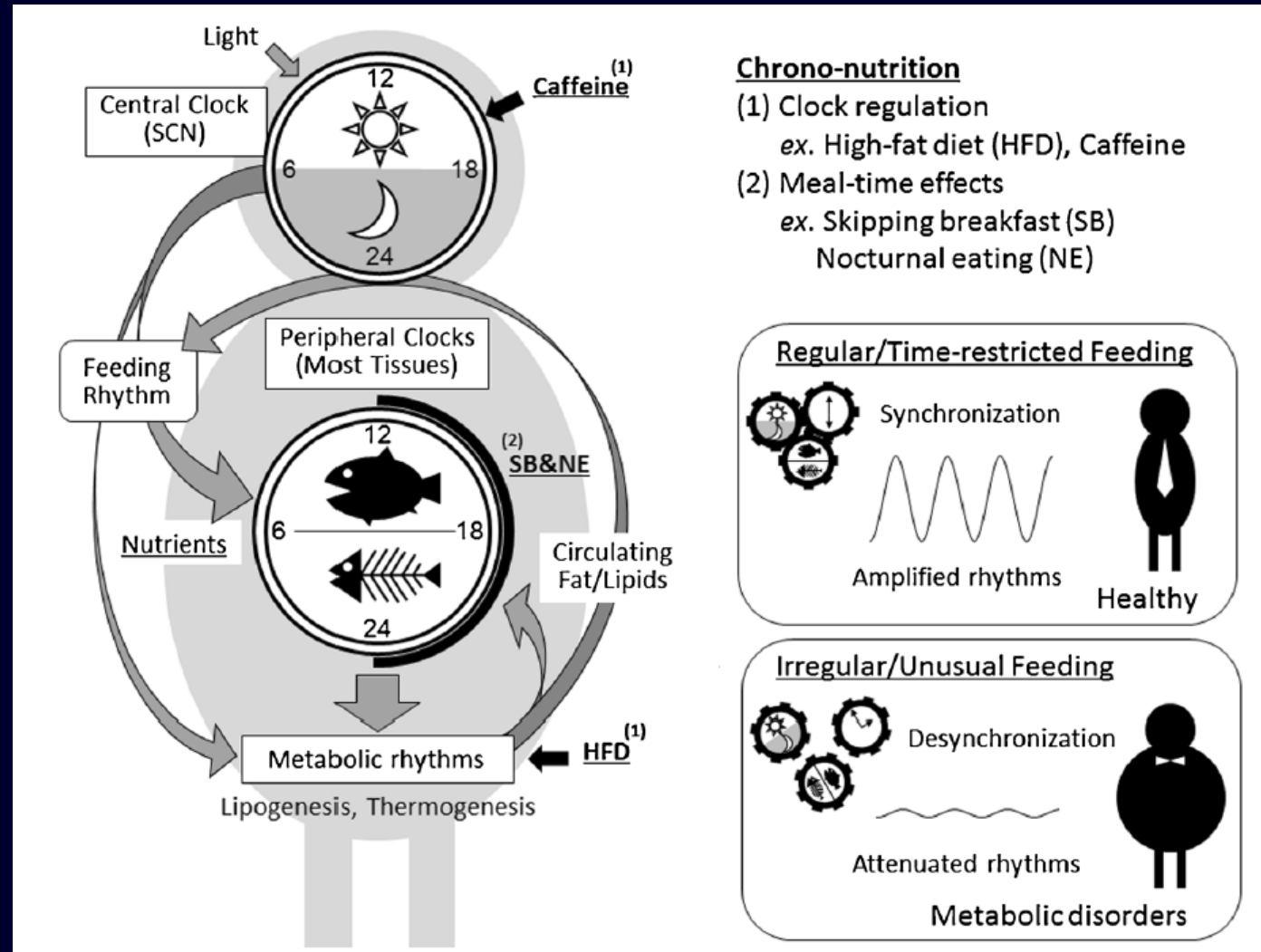
# Circadian rhythm & reduced estrogen

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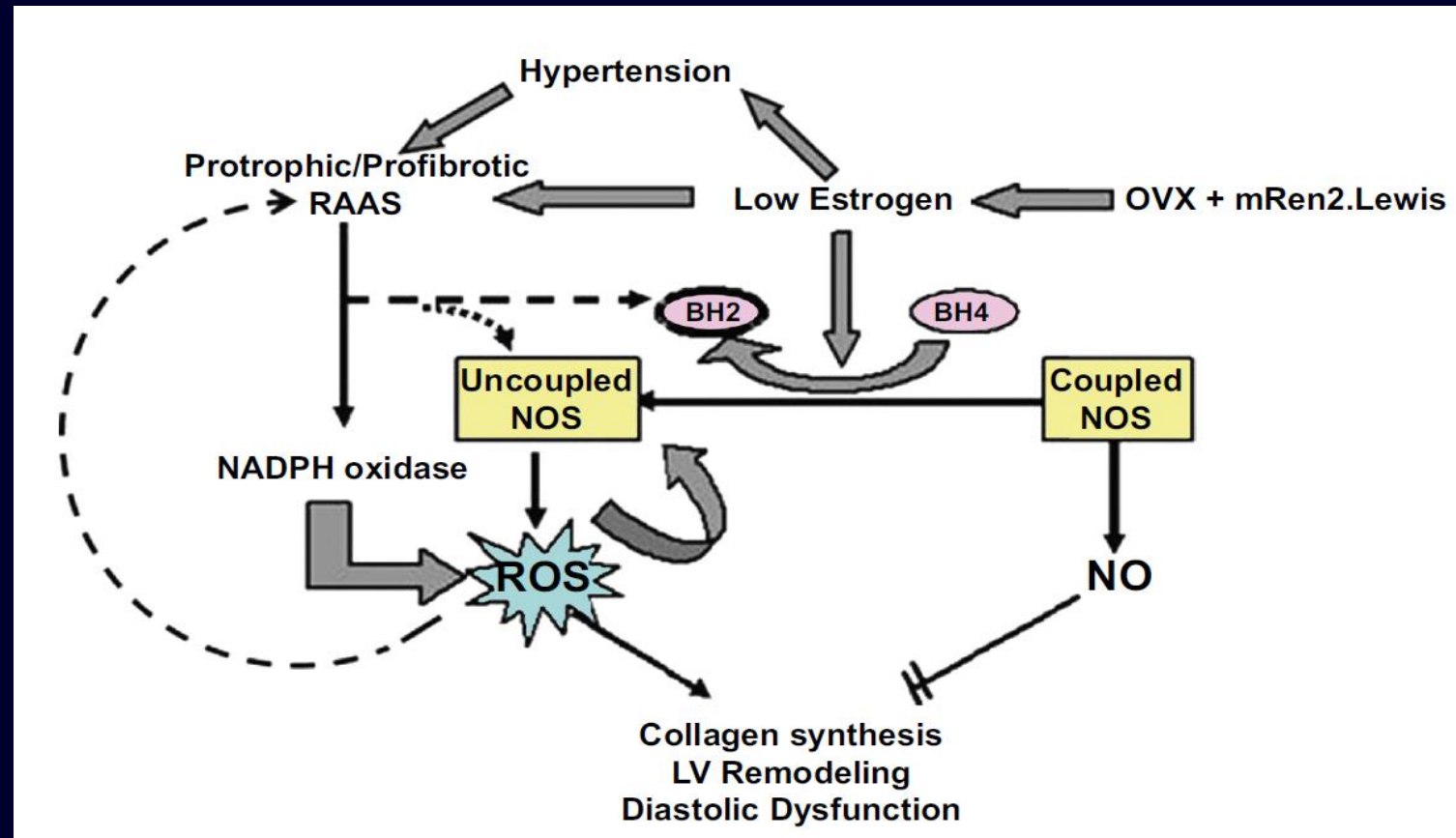
## INFLAMMATION

- Atherosclerosis and cardiovascular disease
- Metabolic alterations and altered appetite – weight gain
- Impaired cognition
- Immune system alterations
- Reduced energy
- Significant reduction in neurotransmitter production – melatonin and serotonin - poor sleep quality, oxidative stress, mood alterations

# Circadian rhythm and intestinal rhythms



# Your patient is menopausal ... NOW WHAT DO YOU DO??



# Deal with what is modifiable

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## Non-modifiable Risk Factors

- ✗ Age
- ✗ Gender
- ✗ Race
- ✗ Menopausal status
- ✗ Family history: Parental history of CAD increases a women's risk by 70%

## Modifiable Risk Factors

- ✓ Diet choices and meal timing
- ✓ Sleep time and quantity
- ✓ Circadian rhythm influencers
- ✓ Stress management
- ✓ Physical activity level
- ✓ Hormone use
- ✓ Tobacco and drug use
- ✓ Supplements

# Where to begin?

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1. Laboratory Testing
2. Exercise
3. Diet
4. Supplements



# Key cardiovascular testing options

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- Inflammatory markers
- Advanced lipid profile
- Insulin and HbA1c
- Oxidized LDL
- Ferritin
- ApoE and MTHFR
- B12 and Homocysteine
- 25 OH Vitamin D
- Omega Check
- Uric acid
- Heavy metals
- Thyroid: TSH, Free T3, Free T4, Anti-TPO, Thyroglobulin antibodies
- Testosterone, DHEAS, Pregnenolone
- Other micronutrients



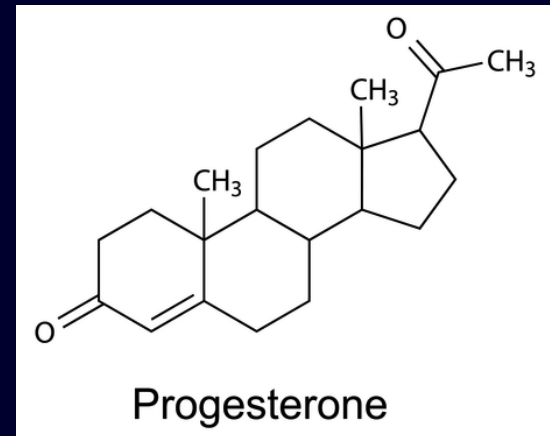
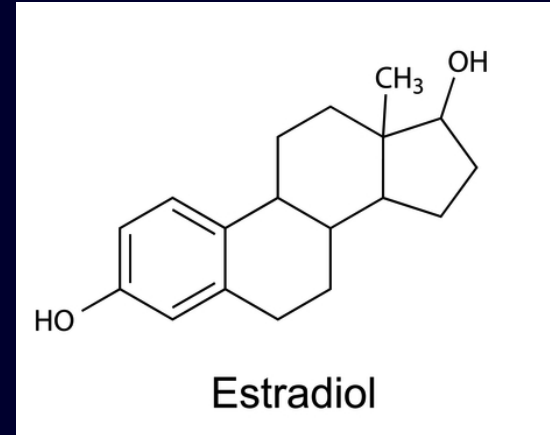
# Hormone therapy revisited

## Conventional HRT

- Estradiol patch or gel
- Oral micronized progesterone (preferably cyclic)

## Rhythmic HRT

- Estradiol and progesterone creams
- Applied twice daily with variable dosing to mimic a normal menstrual cycle





# Exercise

- Regular exercise contributes to:
- Lower blood pressure
- Lower blood glucose levels
- Improved lipid profiles
- Healthy body weight
- Improves microbiome diversity
- Resets the circadian clocks

**Sedentary elderly adults had decreased NO-mediated vasodilator function, compared to age-matched active adults.**

**Exercise reversed impaired microvascular NO function in sedentary adults!**



# Diet

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Begin with a **vegan** diet -- 10–12 servings vegetables, 2 fruit

The **Modified Mediterranean Diet** (leave out all or most dairy and gluten) supports healthy lipid levels (raises HDL & lowers TG) in postmenopausal women - reduces risk of obesity, hyperglycemia & CVD

Eat foods that support the **microbiome!**

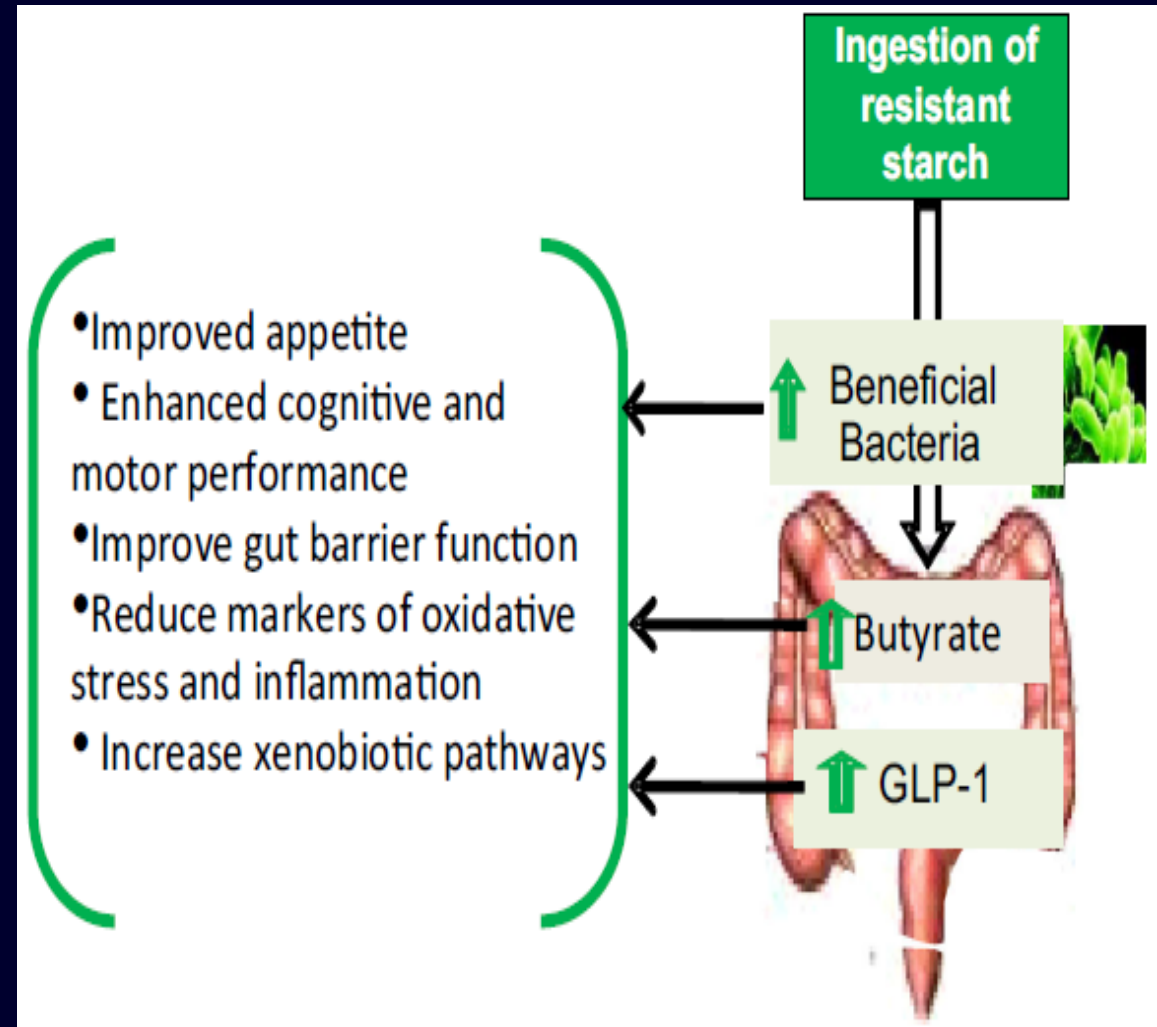
- Prebiotics and Probiotics
- Complex fiber-rich carbohydrates
- Polyphenol-rich foods

**Fasting & Time Restricted Eating**



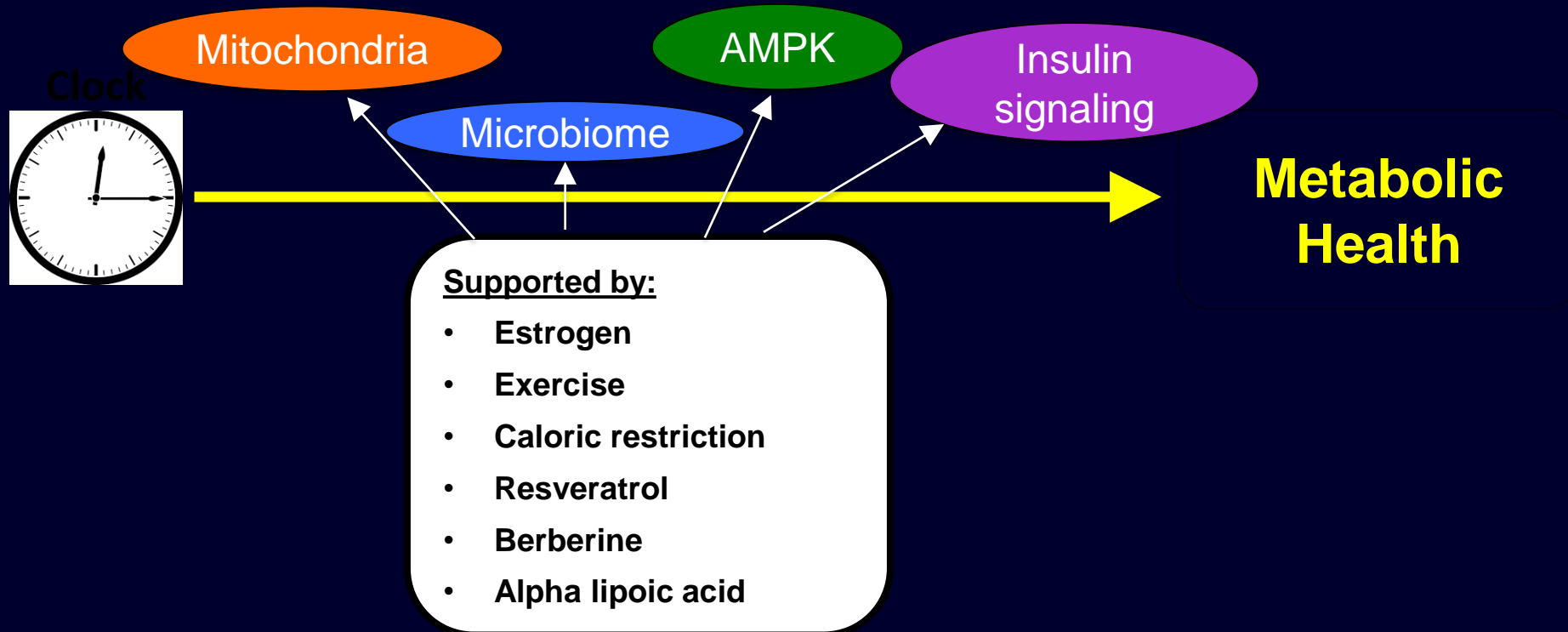
# Benefits of high-amylose starch

- Fiber intake is lower than recommended
- High-amylose starch
  - 40-60% fermentable carbohydrate
  - Amylose can be fermented
- Biological impact
  - Enhances gut microbiota profile and production of short-chain fatty acids
  - Improves gut barrier function
  - Mimics effects of caloric restriction



# Support metabolic health

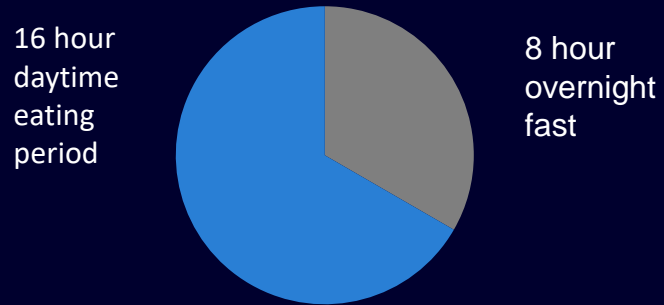
## Systems & pathways involved



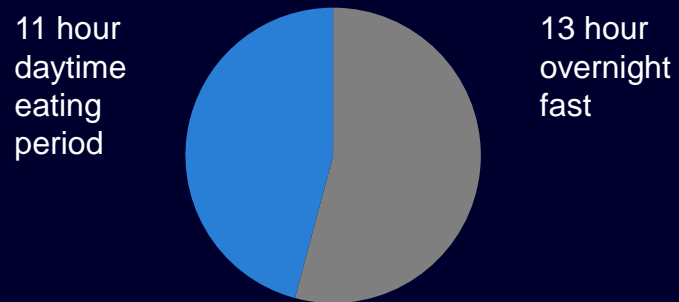
# Correct the clock: meal timing

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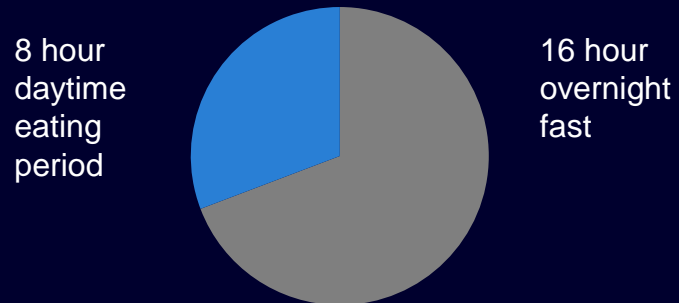
Typical American Meal Pattern



Circadian-Aligned Meal Pattern (A)



Circadian-Aligned Meal Pattern (B)



- Eat dinner early
- Eat at approximately the same times each day
- Limit snacking
- Consider a daytime fast once or twice per week. Eat larger meals (breakfast and dinner) about 13 hours apart
- Consider intermittent or periodic fasting or a fasting mimicking diet

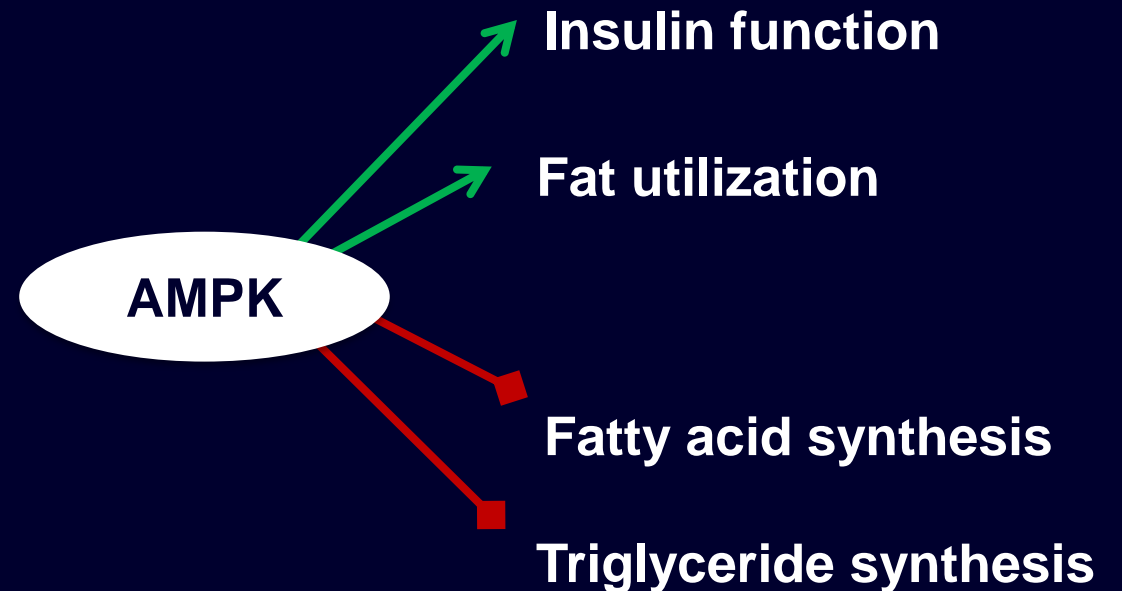
# Correct the clock: meal timing

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## The next best thing: **Fasting mimetics**

Agents that partially emulate the metabolic benefits of fasting by supporting the AMPK pathway.

Resveratrol  
Alpha lipoic acid  
Berberine  
Exercise



# Supplements: key areas of support to address the needs of your menopausal patients

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- Insulin sensitivity & glucose metabolism ← Berberine
- Lipid Profile ← Phytosterols, Bergamot
- Antioxidant status
- Blood flow
- Endothelial function and arterial wall integrity { Citrulline  
Vitamin C  
Taurine  
Magnesium  
Polyphenols

# Phytosterols support a healthy lipid profile

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- Compete with cholesterol for absorption into the body
- Promote excretion of cholesterol via bile acids

**Plant sterol moderated LDL-cholesterol concentrations from baseline by between 15.1% and 26.8%**

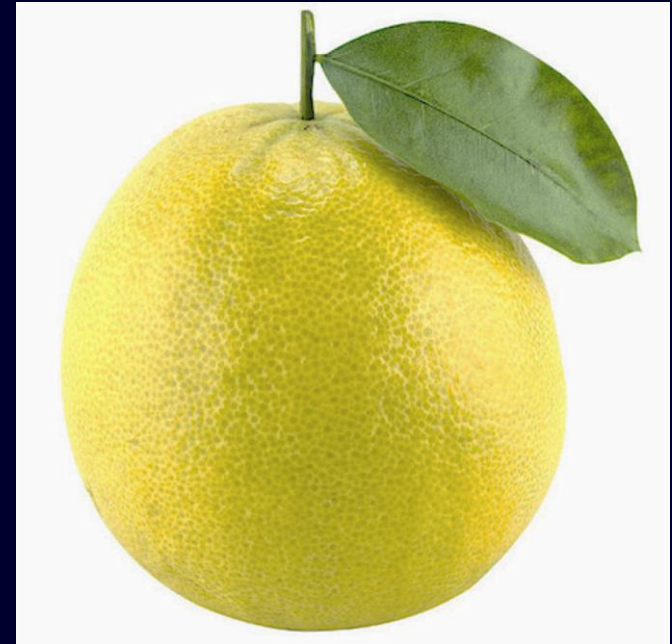
**Meta-analyses of over 40 clinical trials suggest that phytosterols provide significant support for a healthy lipid profile.**



# Bergamot Orange Extract

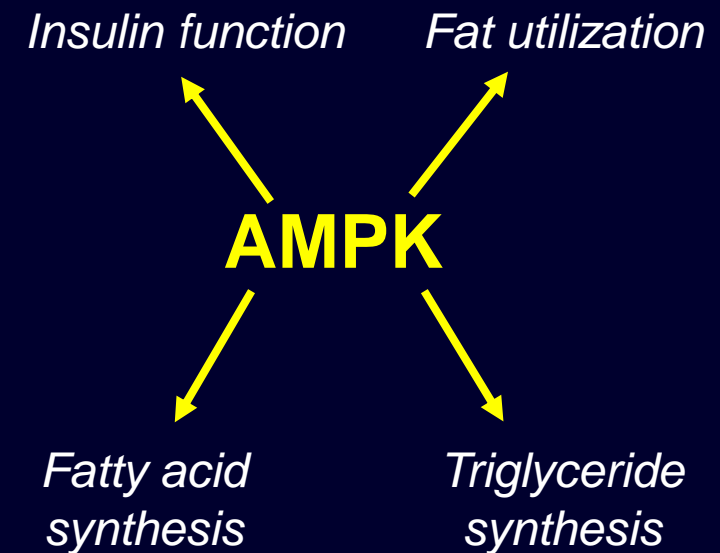
- Bergamot - flavonoids that moderate hydroxymethylglutarate (HMG)-CoA reductase, which promotes lipid biosynthesis

**In animal models, Bergamot maintained healthy lipid, triglyceride and plasma glucose levels in 30 days**



# Berberine supports insulin sensitivity

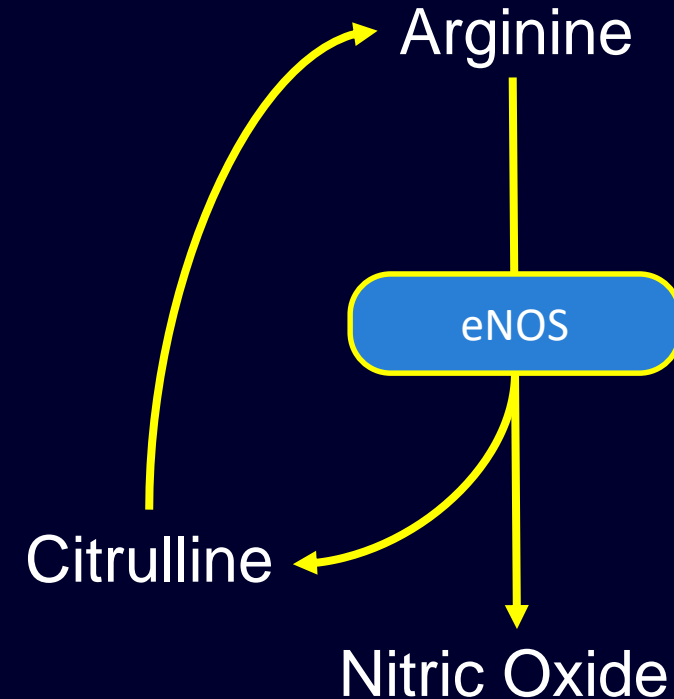
1. Supports glycolysis and enhances GLUT4 translocation, via activation of AMPK
2. Supports the expression of the insulin receptor gene
3. Moderates intestinal absorption of glucose



Over a 3 month period, berberine significantly reduced waist circumference, moderated triglycerides and supported insulin sensitivity

# L-citrulline is more Effective at Increasing Plasma L-Arginine than L-Arginine

- Double-blind, randomized, placebo-controlled crossover study of 20 healthy volunteers
- L-citrulline increased AUC and Cmax of plasma L-arginine more effectively than L-arginine
- L-citrulline increased L-arginine/ADMA ratio, urinary nitrate and cGMP



# Polyphenols

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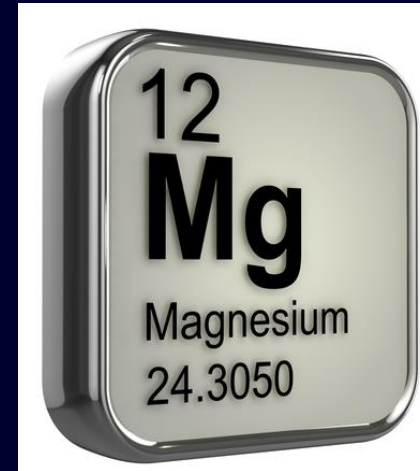
- Key sources: cranberries and grape seeds
- Cranberries and grapes are rich in proanthocyanidins (PACs) and other polyphenols.
- PACs are antioxidants and support mechanisms that are associated with healthy endothelial function.
- PACs protect eNOS and NO from reactive oxygen species



# Magnesium

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- Essential roles in vasomotor function:
- Regulation of calcium channels
- Production of nitric oxide
- Prostacyclin formation
- Preferred form – magnesium glycinate; well tolerated, highly bioavailable



# Case study: Katherine M.

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## Background

- 50 years old year woman G3 P2 SAB1

## Presenting Complaints

- Periods have been irregular over the past 3 years, varying from 1-4 months apart – now none for 9 months
- Had been healthy with no significant medical history
- Eats mostly home cooked foods, little processed food
- Difficulty sleeping over past 2 years
- 8 pound weight gain in past year, 5 over previous 2 years
- Binges on snack food late at night, feels best at night and gets very hungry, very fatigued in the morning
- Heartburn, fatigue, mood swings, hot flashes, low sex drive, foggy brain

# Case study: Katherine M.

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## Lab Results

- Insulin resistance – Pre DM, elevated triglycerides, normal cholesterol, mild inflammation, borderline low thyroid
- Adrenal Stress Index: Low morning cortisol, high evening levels: **Flipped circadian rhythm**
- FSH, estradiol in menopausal ranges
- Testosterone – low end of reference range

## Therapeutic Program Initiated

- **Detoxification:** DIM, probiotics, psyllium, chlorella, EPA/DHA, turmeric extract, broccoli extract, artichoke extract, L-glutamine, NAC, taurine, milk thistle, Calcium-D-glucarate
- **Symptom Management:** Hop extract, 7-hydroxymatairesinol, Ashwagandha, Maca extract, L-theanine, resveratrol, rhodiola rosea,
- **Lifestyle:** Time Restricted Eating, mild Exercise Program, sleep hygiene, stress control program (Guided Imagery, Tapping, Progressive Relaxation)

# Case study: Katherine M.

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## After Initial 4 weeks:

- Felt “enormously better”
- Cravings, snacking and night eating nearly completely resolved
- Lost 6 pounds
- Sleeping much better but still some hot flashes – but much reduced
- More energy
- Brighter outlook on life
- Minimal heartburn
- Decided to begin bioidentical hormone therapy

## Therapeutic Program Continued – Next Phase

- Bio-identical hormones
- Continue initialization protocol
- Cardiometabolic: Berberine HCl, chromium, ALA, magnesium glycinate
- Stress/Mood/Sleep: L-theanine, magnesium glycinate
- Polyphenol blend for daily wellness and neurocognitive/cardiometabolic support (resveratrol, pomegranate, cranberry, Acai, blueberry, green tea)



## Case Study: Katherine M.

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### 6 months later

- Lost 18 pounds total
- All metabolic tests were now in the normal range
- Sleep much better
- Hot flashes entirely resolved
- Exercising regularly
- Good sex drive
- Great energy
- Great focus

***“I feel like  
my old  
self.”***

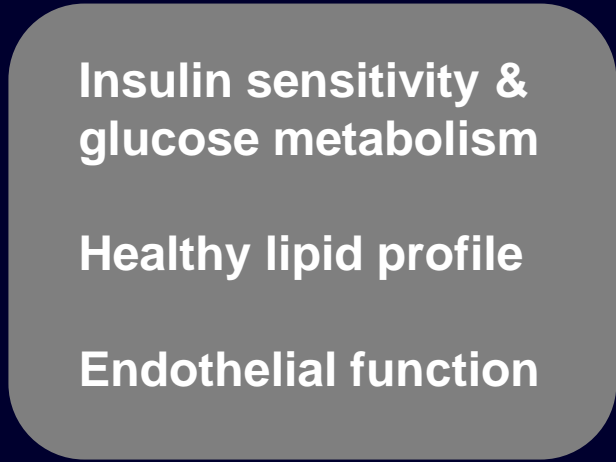
# Modifiable through diet, lifestyle, & supplementation

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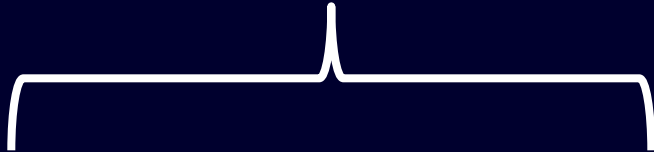
Menopause



Estrogen

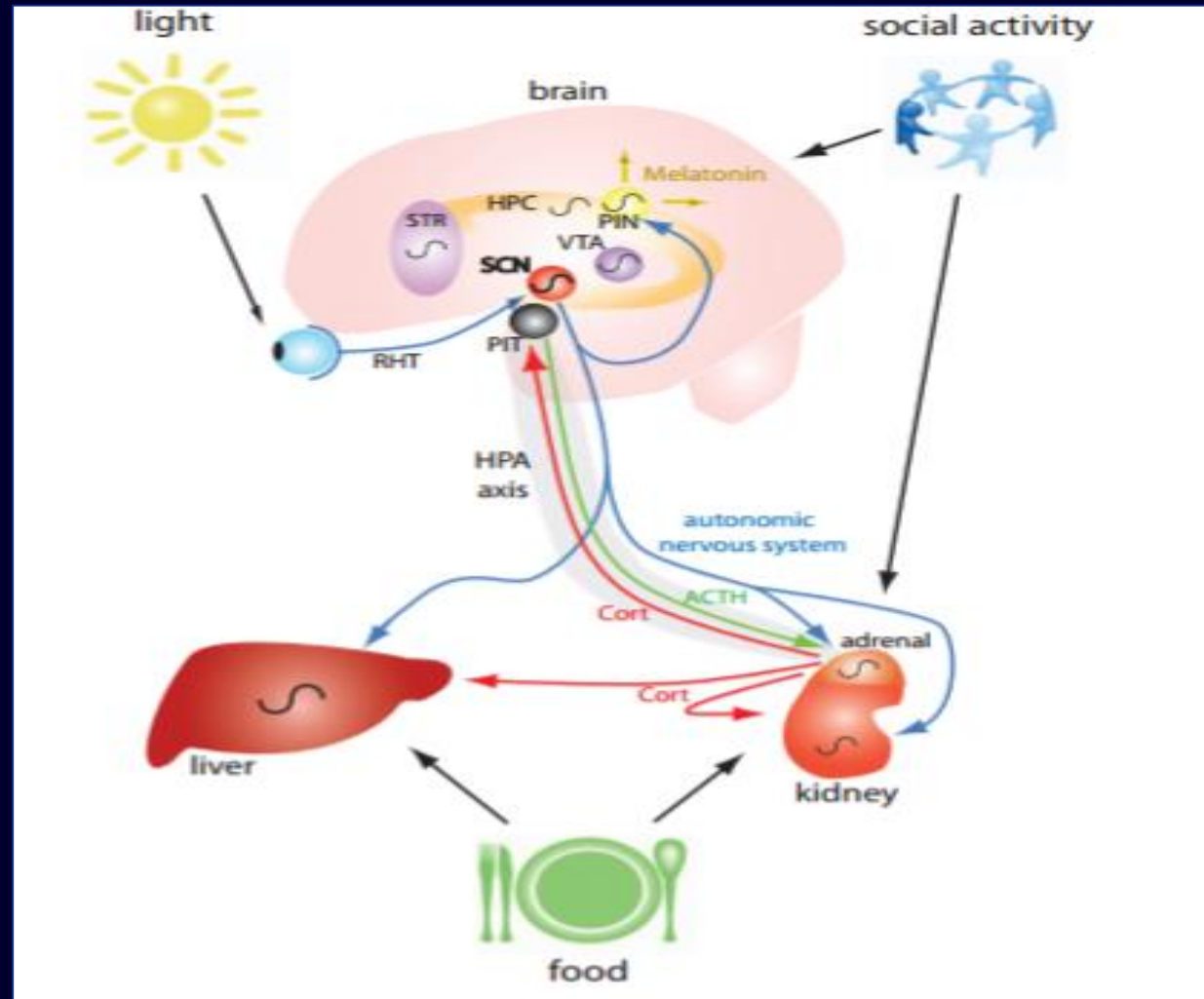


Cardiovascular health



Supported by diet, lifestyle, and supplementation

# Living to the beat: maintain metabolic & cardiovascular health



# Thank You

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