



***PCOS – The perfect female storm:  
When reproduction meets metabolism***

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**⑩ Financial Disclosure-No Relevant Relationships  
with a Commercial Interest to Disclose**

# Learning Objectives

- Analyze the interplay between metabolic and reproductive health and their relationship to PCOS
- Recognize the role of estrogen and its receptors on the manifestations of PCOS
- Compare and summarize the critical roles played by the gut microbiome and the circadian rhythm in the development of PCOS
- Develop an efficacious, holistic, and therapeutic approach to address PCOS

# Women's Optimal Health = Optimized Hormones

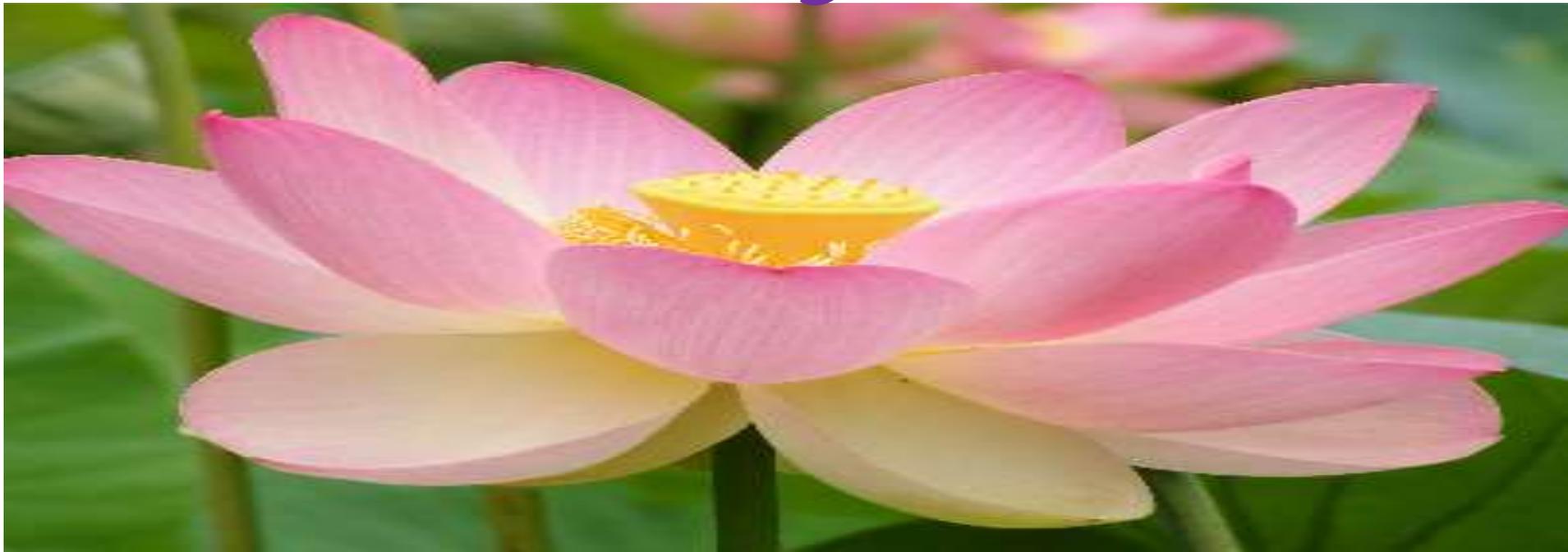


**Prime Directive of Life:**

*Reproduction and survival*

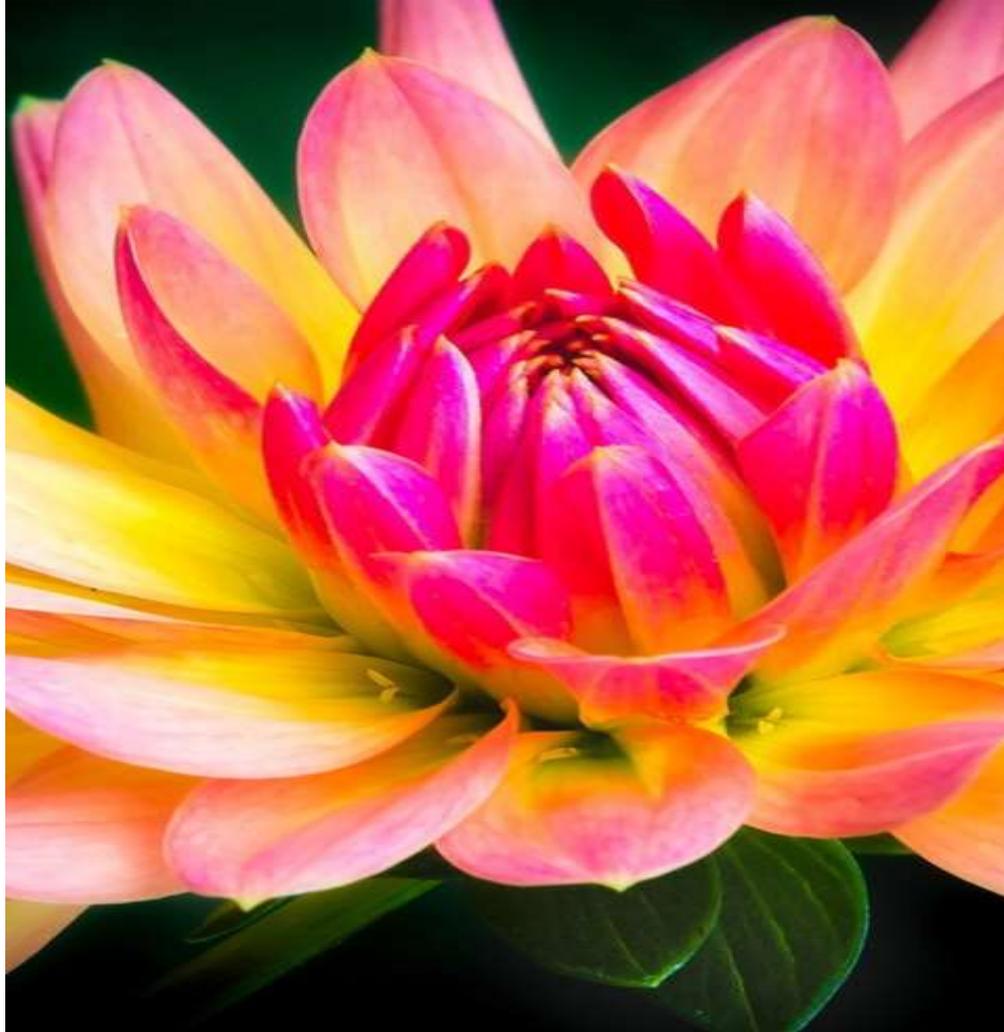
*and then to repeat the process*

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





# The Personal Face of PCOS



# Lori's Story of PCOS: Pain & Suffering

Acne

Hirsutism

Alopecia

Irregular  
cycles

Obesity

Fatigue

Joint pains

Gingivitis

Depression

IBS



# *What's Changed?*

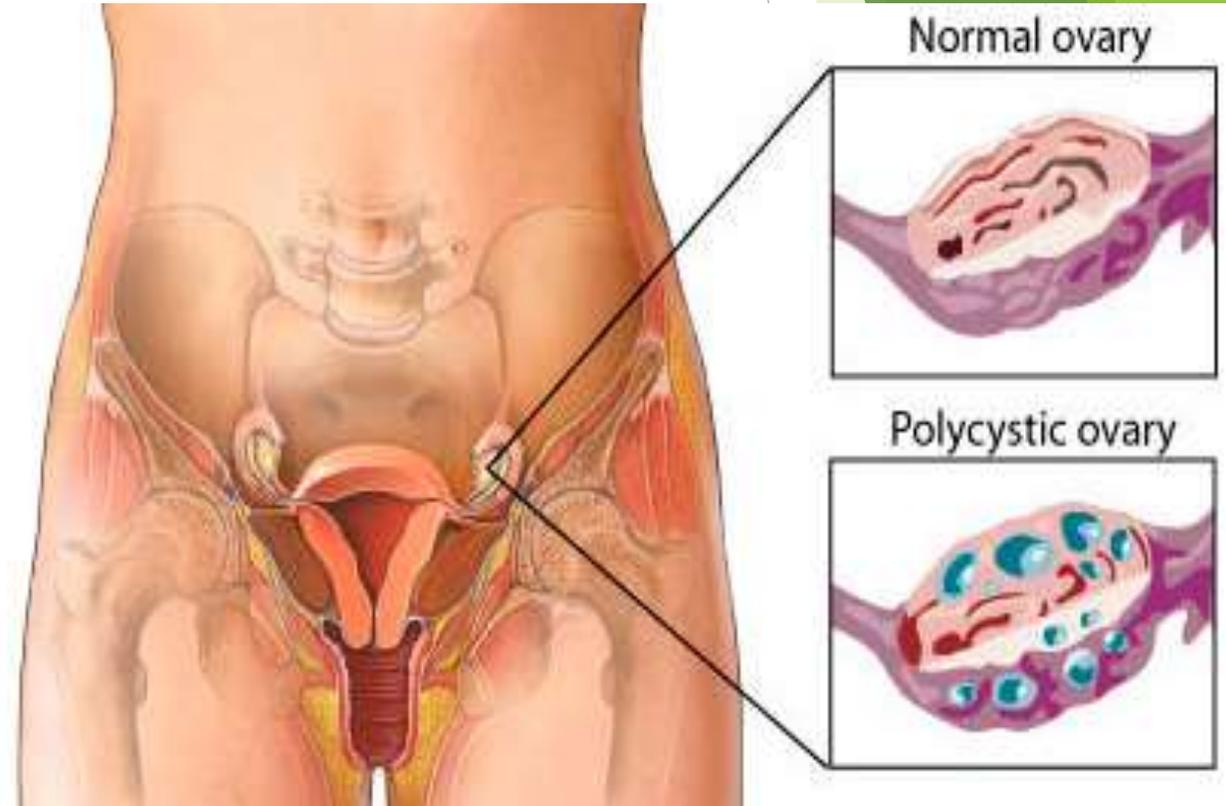


Nestler JE. *N Engl J Med.* 2008; 358: 47-54.

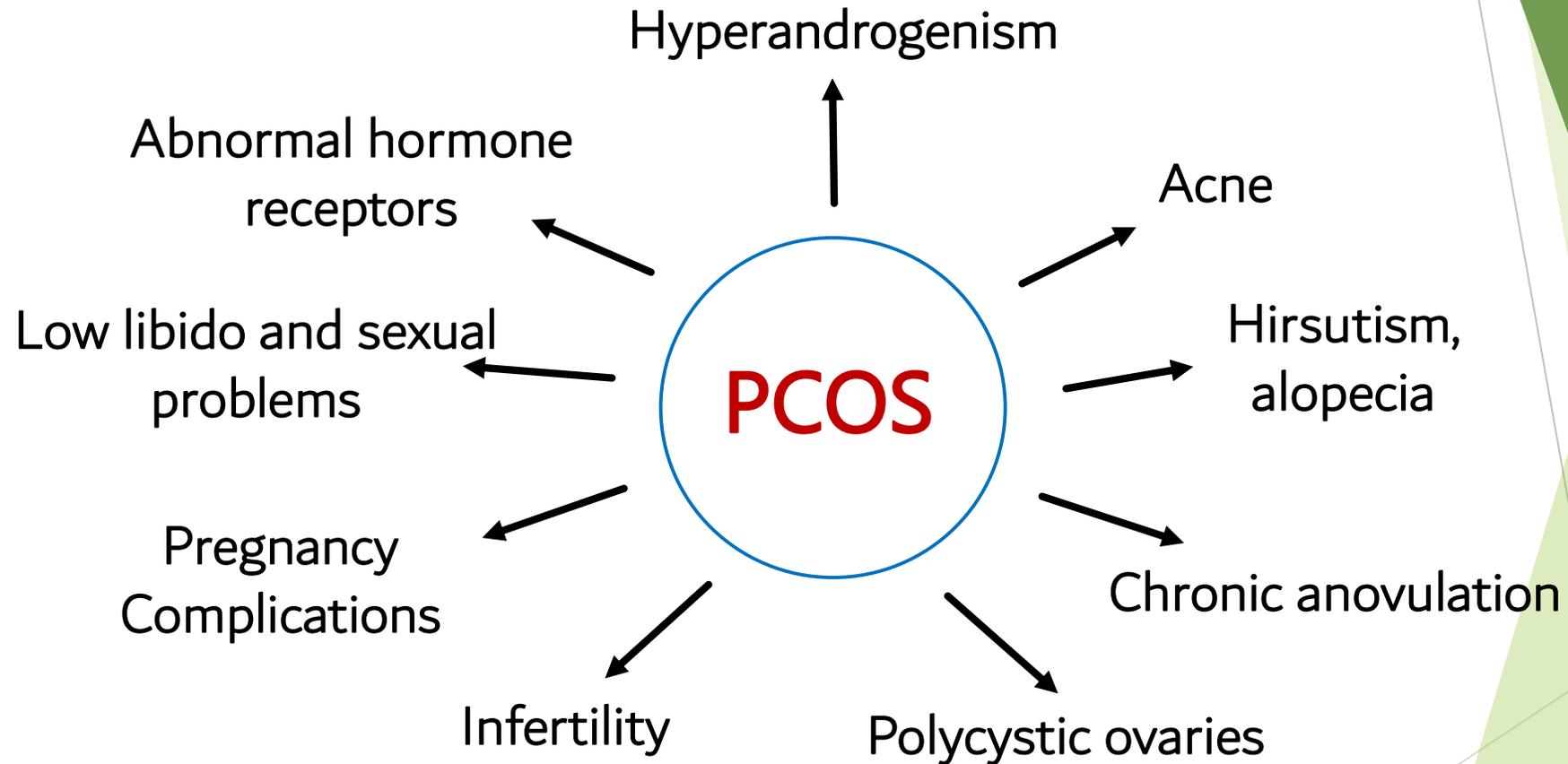
# Polycystic Ovary Syndrome (PCOS)

*Blending the Role of Hormones,  
Circadian Rhythm, Environmental  
Toxicants, and Cardio-Metabolic Health*

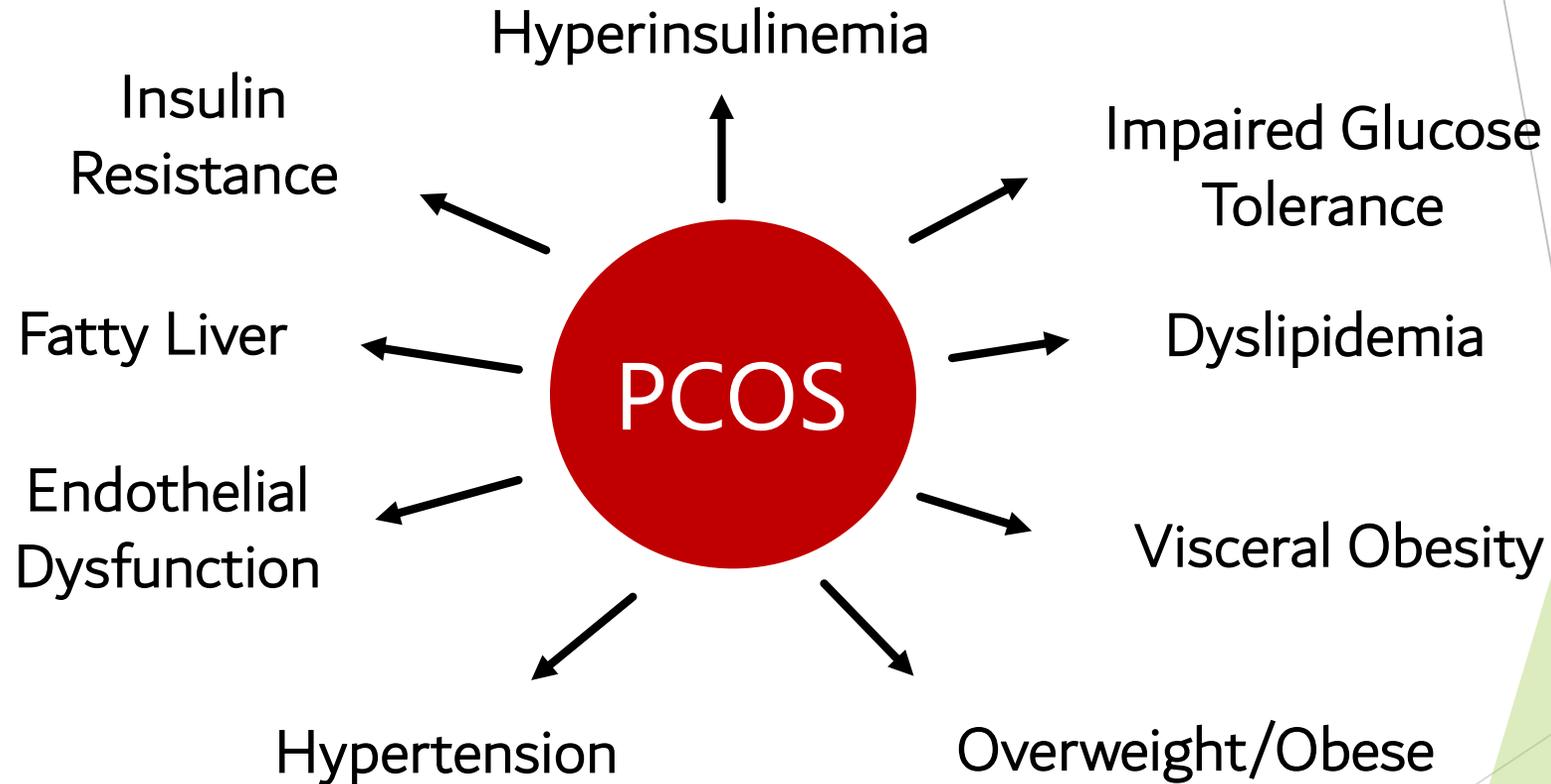
- A hormonal disorder, becoming obvious after puberty
- Characterized by the proliferation of small cysts in the ovaries
- The most common endocrine dysfunction of women



# Hormonal/Reproductive Effects of PCOS



# Metabolic Effects of PCOS



# Other Associated Conditions

**Autoimmune disease (especially thyroid)**

Skin tags and darkened skin (acanthosis nigricans)

Gastrointestinal problems (IBS, leaky gut)

Arthritis and tendinitis

Depression, anxiety, stress

Vaginal infections

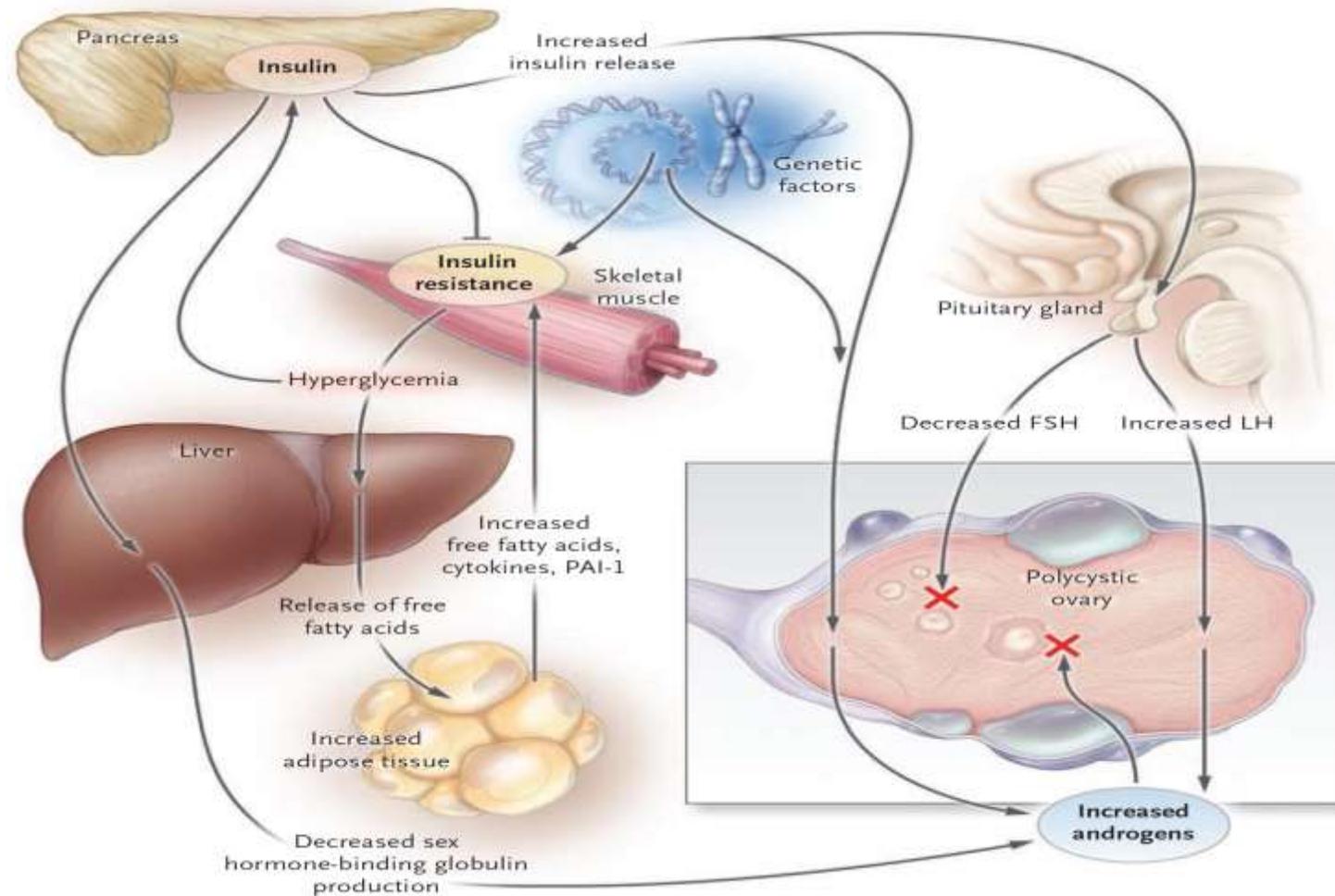
Sleep dysfunction and OSA

Cancer



# Dysregulated Hormones & Metabolism

Dysregulation of various hormonal and metabolic processes



# Etiology of PCOS

## *Complex interaction between genetics & the environment*

### ▶ **Prenatal risk factors:**

▶ Exposure to hormonal fluctuations, EDCs (Bisphenol A) and oxidative stress in-utero

### ▶ **Adult exacerbation with:**

▶ Hormonal imbalances

▶ Chronic inflammation

▶ Metabolic dysfunction

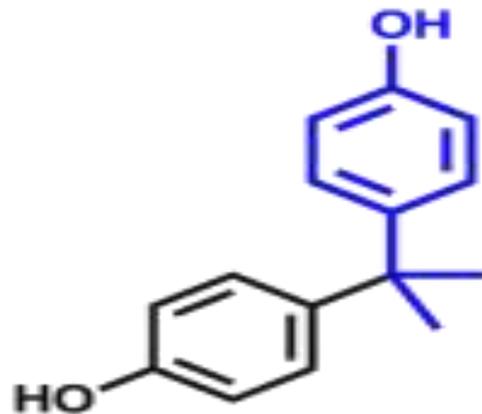
▶ GI imbalances

▶ Circadian rhythm dysfunction

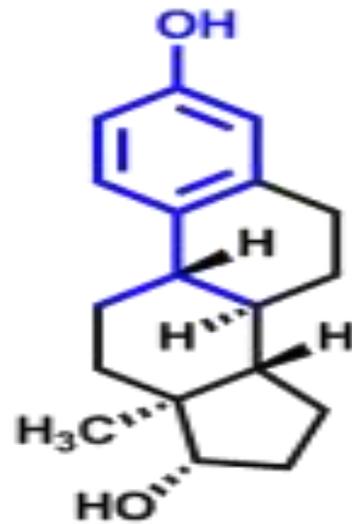


# Endocrine Disruptors

Similar in structure to E2-can  
bind to multiple targets inside  
and outside the nucleus



**Bisphenol-A (BPA)**



**Estradiol**



# Dysregulated Hormones

## *Alteration of estrogen receptor function in women with PCOS*

1. E2 Receptor Beta expression significantly higher than E2 Receptor Alpha
2. E2 Receptor Beta is lower compared to levels of controls
3. E2 Receptor Alpha is lower than levels found in controls

ESTROGEN

# Major Overlooked Factor in PCOS



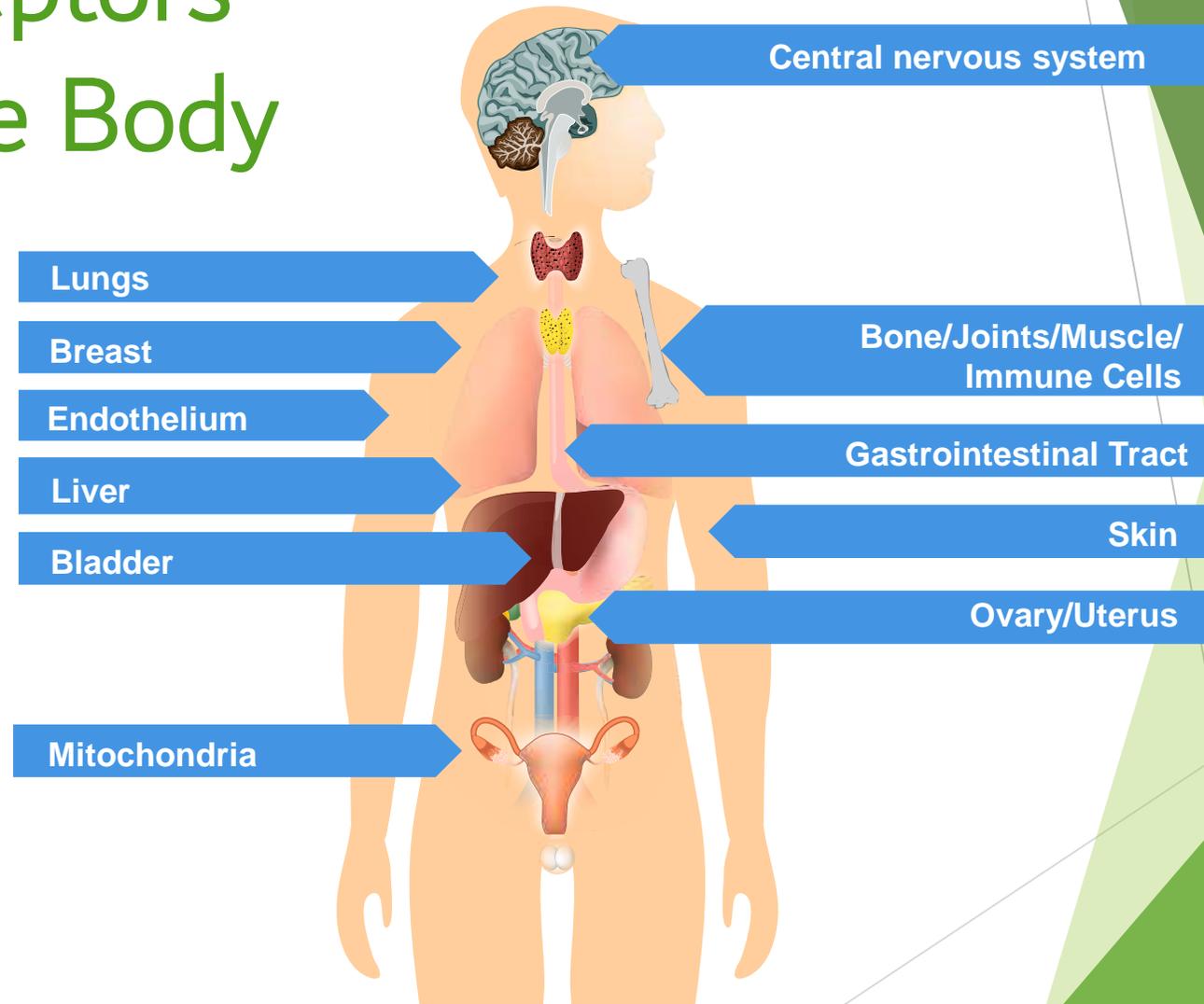
# *REMINDER:*

Estrogen is classically thought of as a reproductive hormone...

*But it has always been about metabolism AND reproduction*



# Estrogen Receptors Throughout the Body



# Estrogen: Concentration Matters

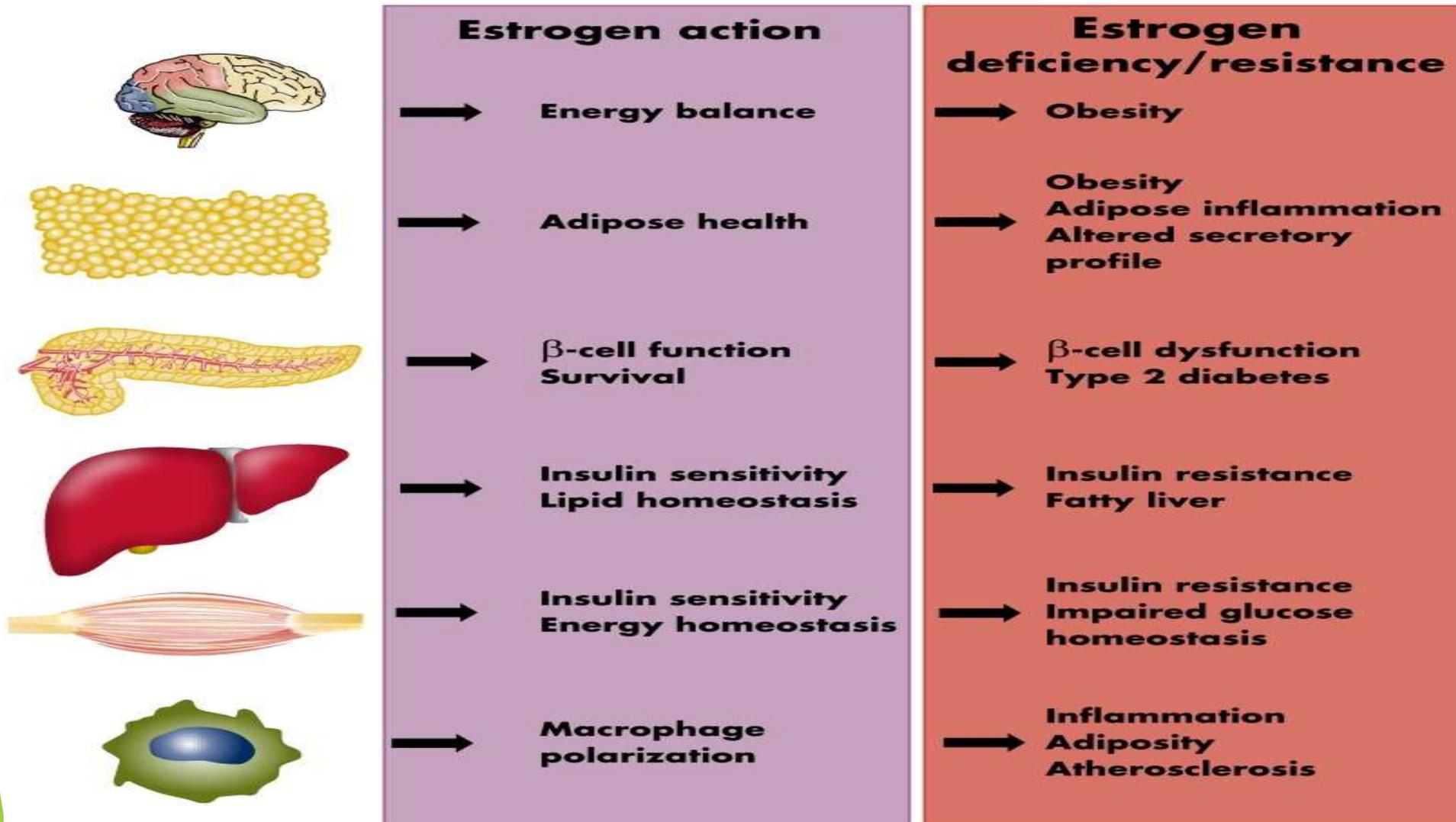
- ▶ “E2 has a bi-potential effect on monocytes and macrophages.
- ▶ Low doses enhance the production of pro-inflammatory cytokines while high doses reduce the production of these cytokines”

***Modulating inflammation  
is a key function of  
ESTROGEN!***

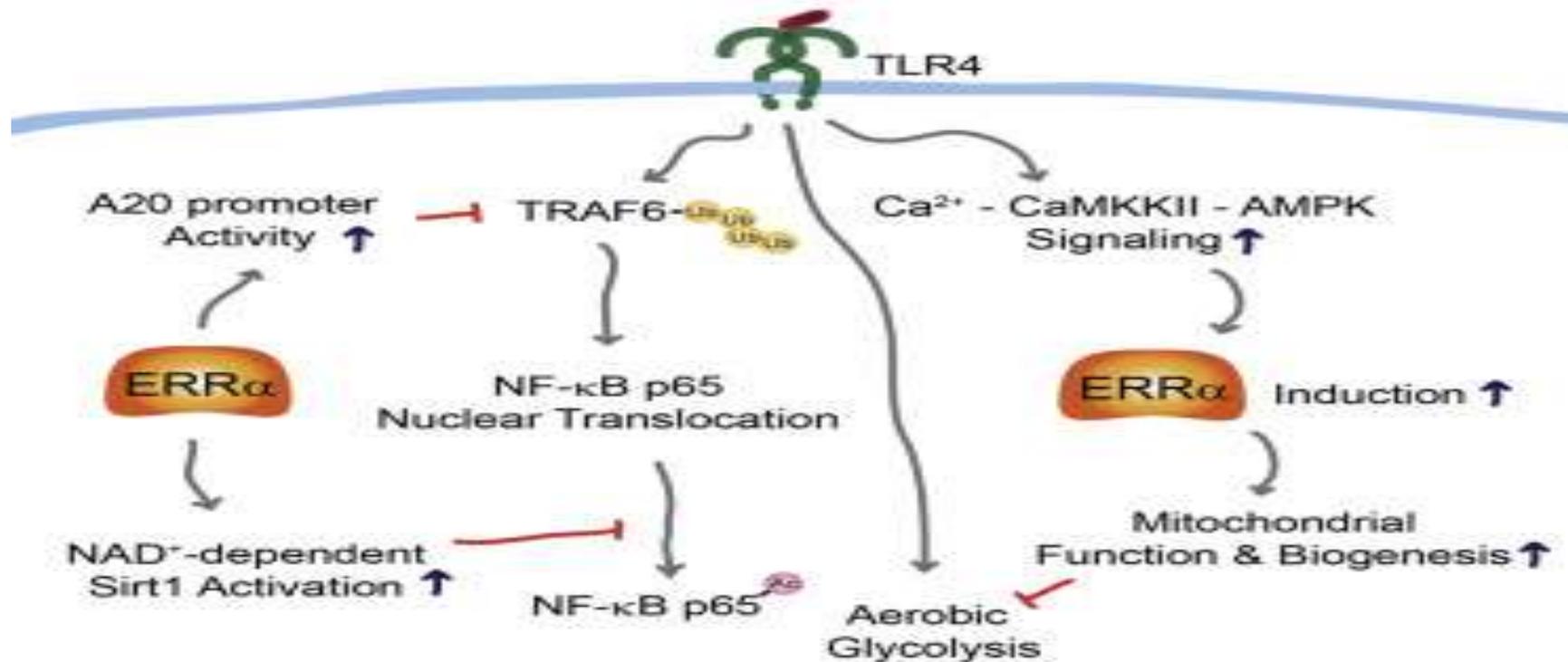
Lateef A and Petri M. J of Autoimm. 2012; 38(1):7-17.

Klein S and Flanagan K. Nat Rev Immunol. 2016 Oct 16(10):626-38..

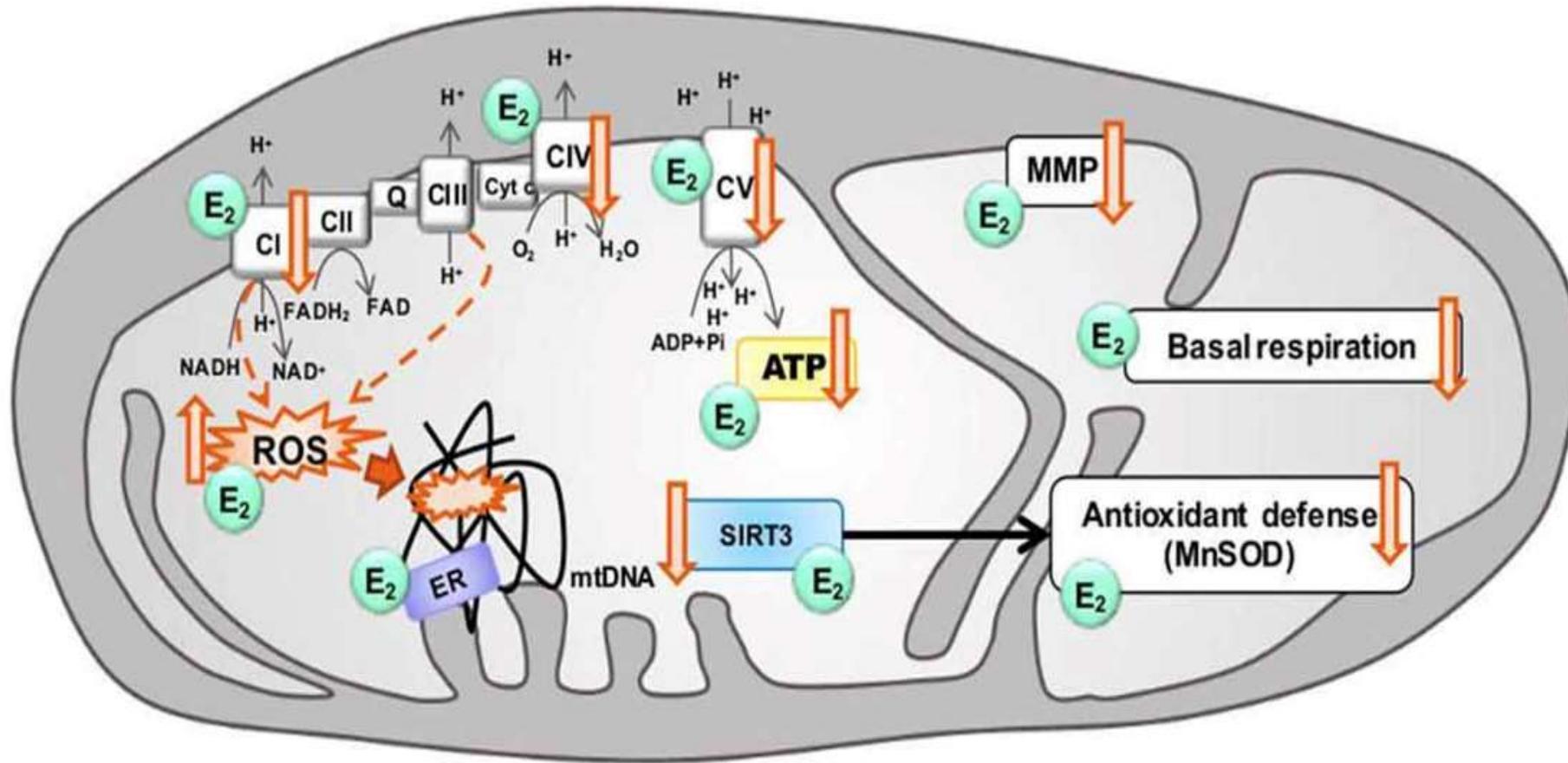
# Consequences of Estrogen Deficiency



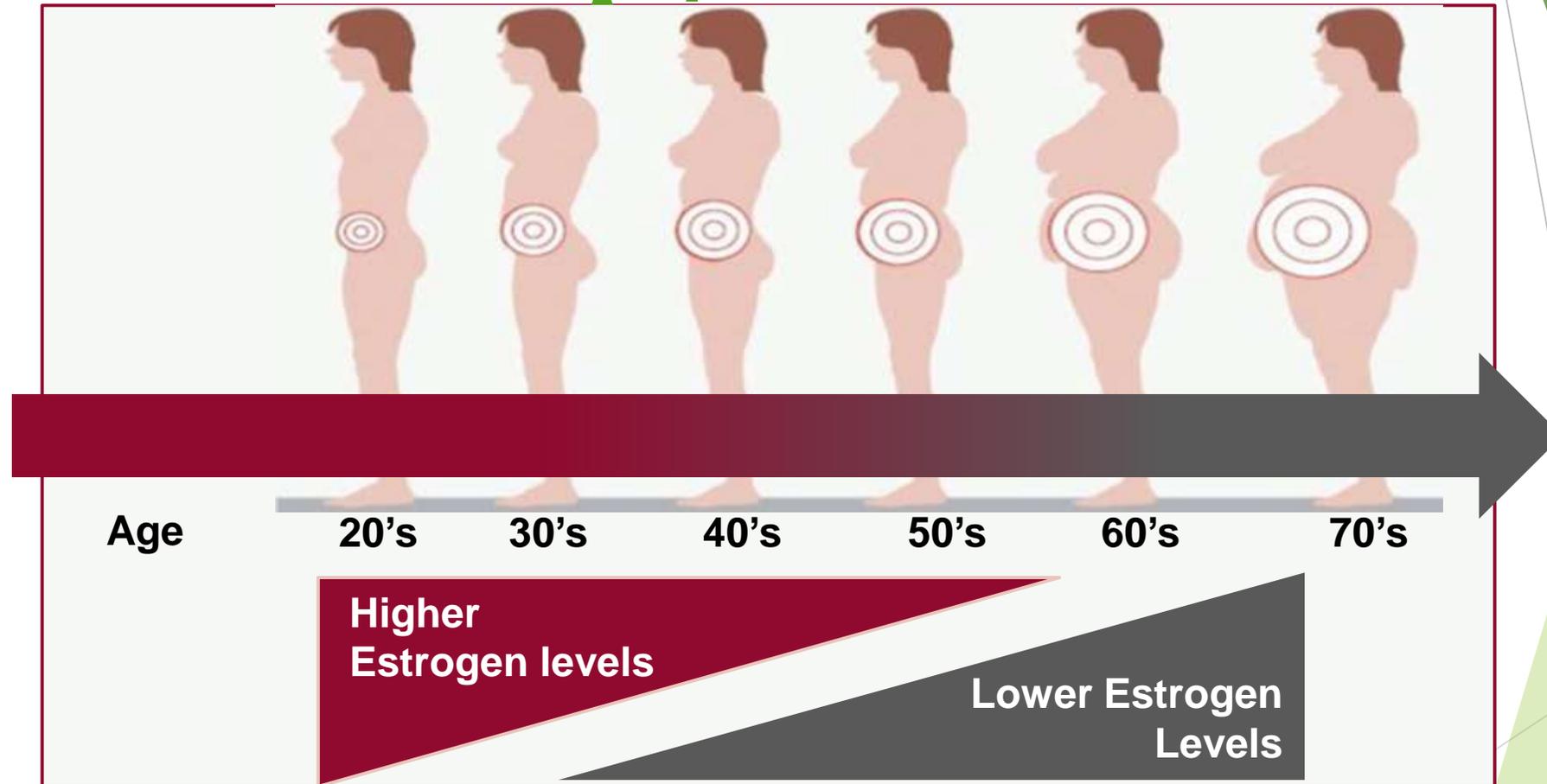
# Estrogen Maintains NAD levels and Activates SIRT1 to Reduce Inflammation



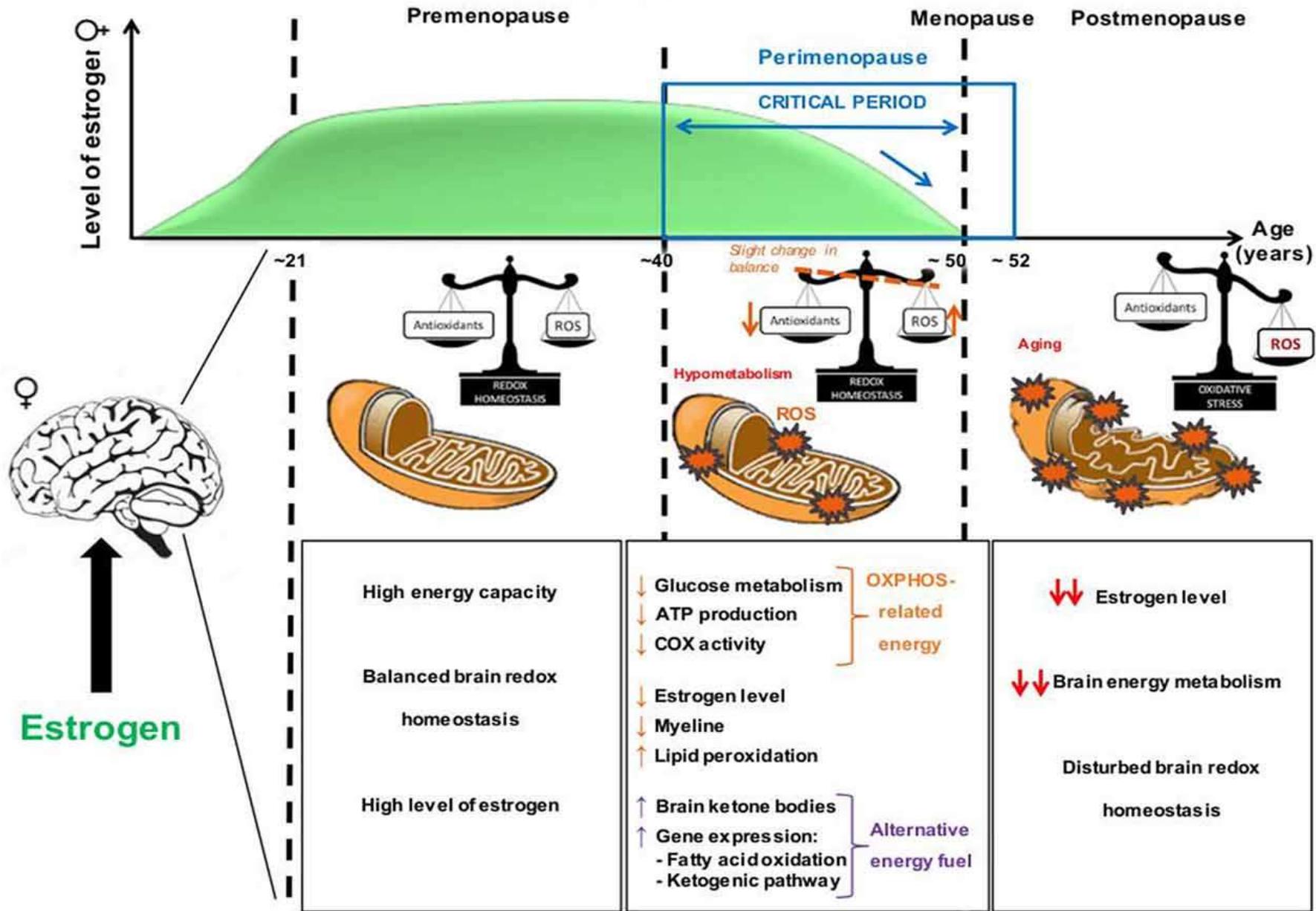
# Estrogen – Mitochondria – SIRT3



# Age-Dependent Shift in Estrogen Levels: PCOS is Like Premature

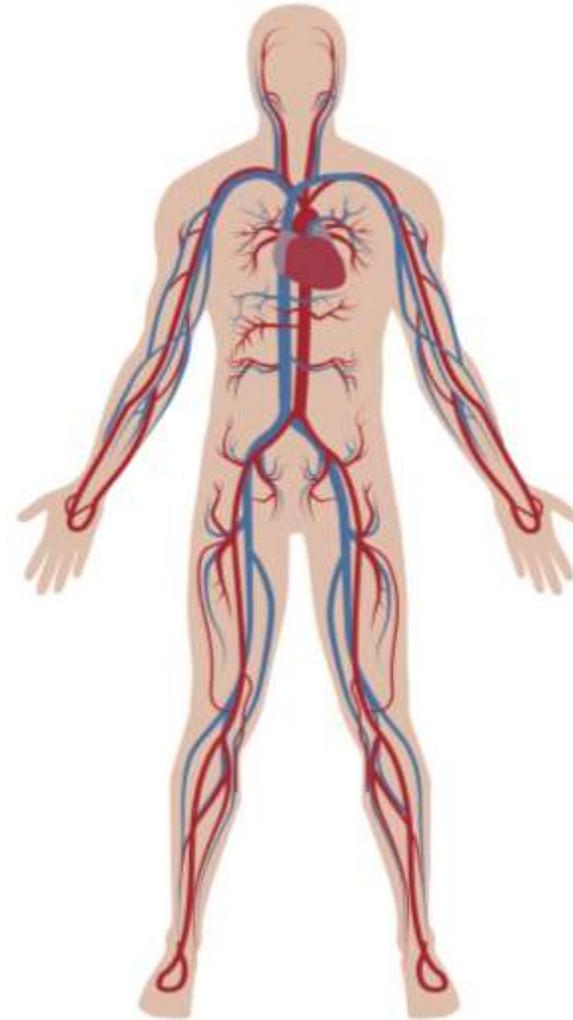


# REPRODUCTIVE SENESCENCE



# Nitric Oxide is Reduced in PCOS

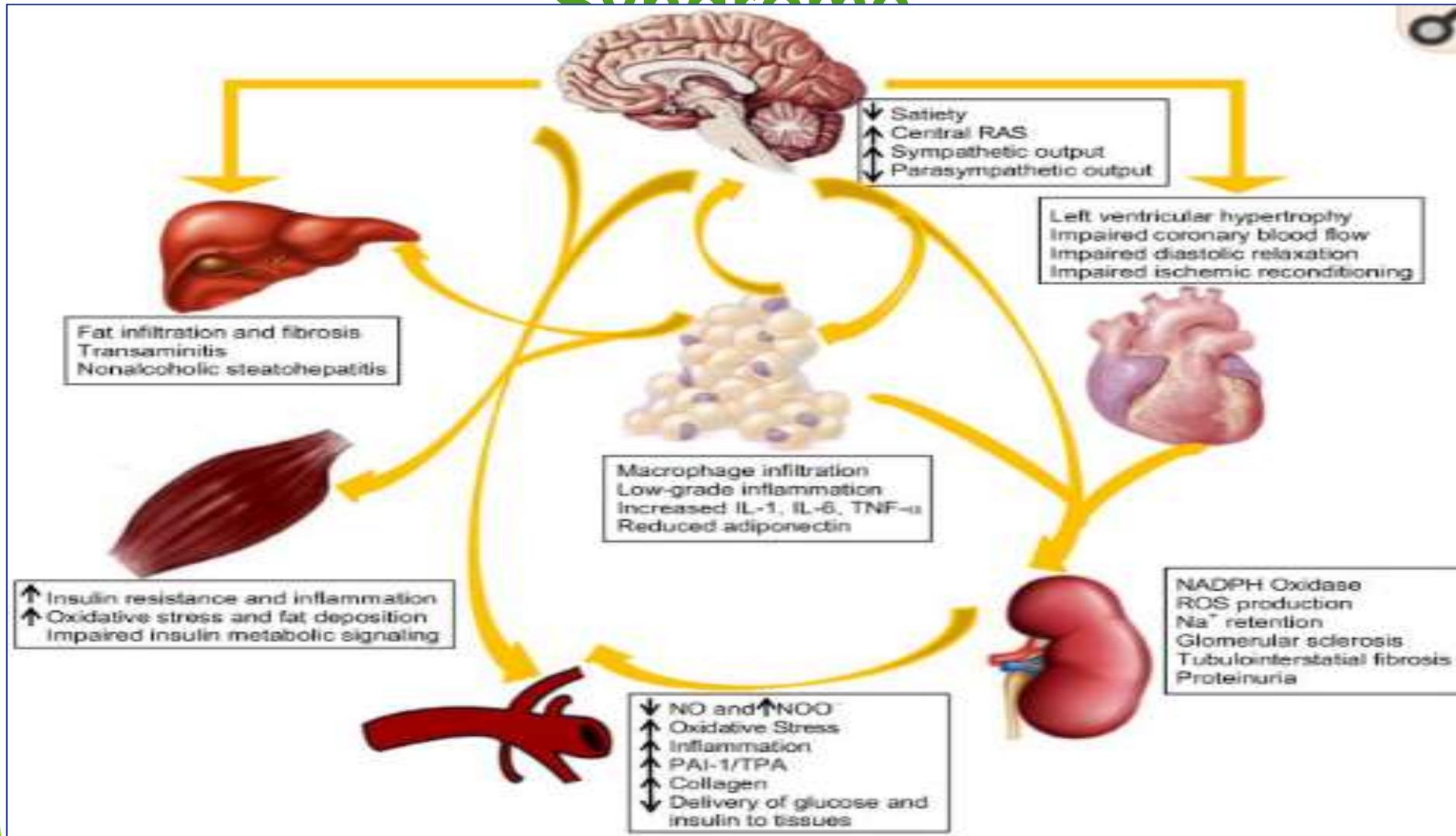
- **T-Regulatory cells (Tregs) lowered in PCOS**
- **NO regulates Treg generation**
- **Markers of lowered levels of iNOS and eNOS in peripheral blood**
- **Higher amounts of ADMA**



# Inflammation: Driving Force of PCOS

- **Dysbiosis - gut, mouth, vagina, skin**
- **Abdominal fat with altered Adipokines**
- **Insulin resistance**
- **Altered immune cell reactivity**
- **Impaired circadian rhythm**

# Cardio-Renal-Vascular-Metabolic Syndrome



# Introducing the Gut Microbiome: *The Unseen Civilization Within Us*

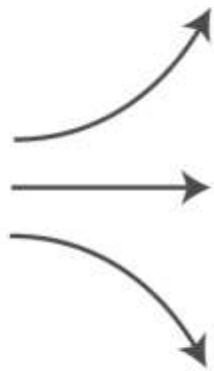


# A Healthy Microbiome Supports all Systems

1. Immune activity
2. Hormone elimination
3. GI integrity
4. Metabolic health



**Healthy  
Microbiome**



Barrier Integrity

Healthy Motility

Reduced  
Inflammation



Metabolic Health

Reproductive Health

Mental Health

Immune Health

# Dysbiosis and PCOS

- ▶ Lower microbial diversity and altered phylogenetic composition
- ▶ Alterations in markers of gut barrier function and endotoxemia
- ▶ Increase in LPS producing bacteria and serum LBP levels

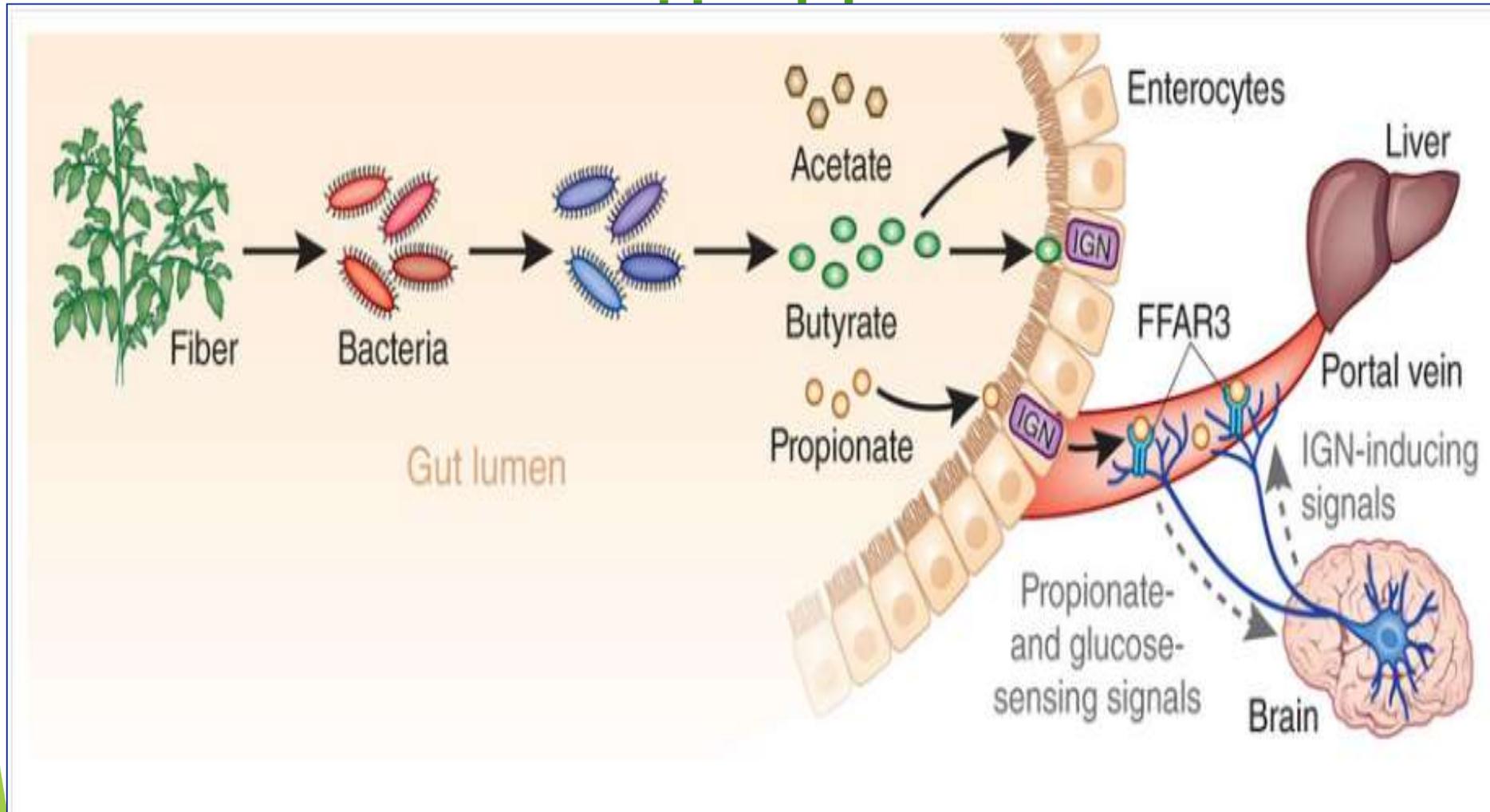
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Lindheim et al; PLOS One. 2017.12(1)

Guo et al ; PLOS One. 2016

Liu et al. Font. Microbiol. 2017;8,324:1-12

# Linking the Microbiome & Short Chain Fatty Acids to Metabolic



# Poor diet + PCOS *drives* Dysbiosis → Systemic Inflammation

High fat/high sugar diet  
leads to Gut dysbiosis ... and

*Circadian Rhythm  
dysfunction*



Guinane CM et al. Tole of the gut microbiota in health and chronic gastrointestinal disease.

Therp Adv Gastroenterol 2013; 6: 295-308

Turnbaugh PJ et al. Diet-induced obesity is linked to marked but reversible alterations in the mouse distal gut microbiome.

Cell Host Microbe 2008; 3: 213-223

**“We are very different animals  
between the day and night”**

## **DAY**

**Eats other organisms  
(plants, animals)  
Active and mobile  
Fully functional  
digestive system  
Prefers carbohydrates  
High metabolic rate**

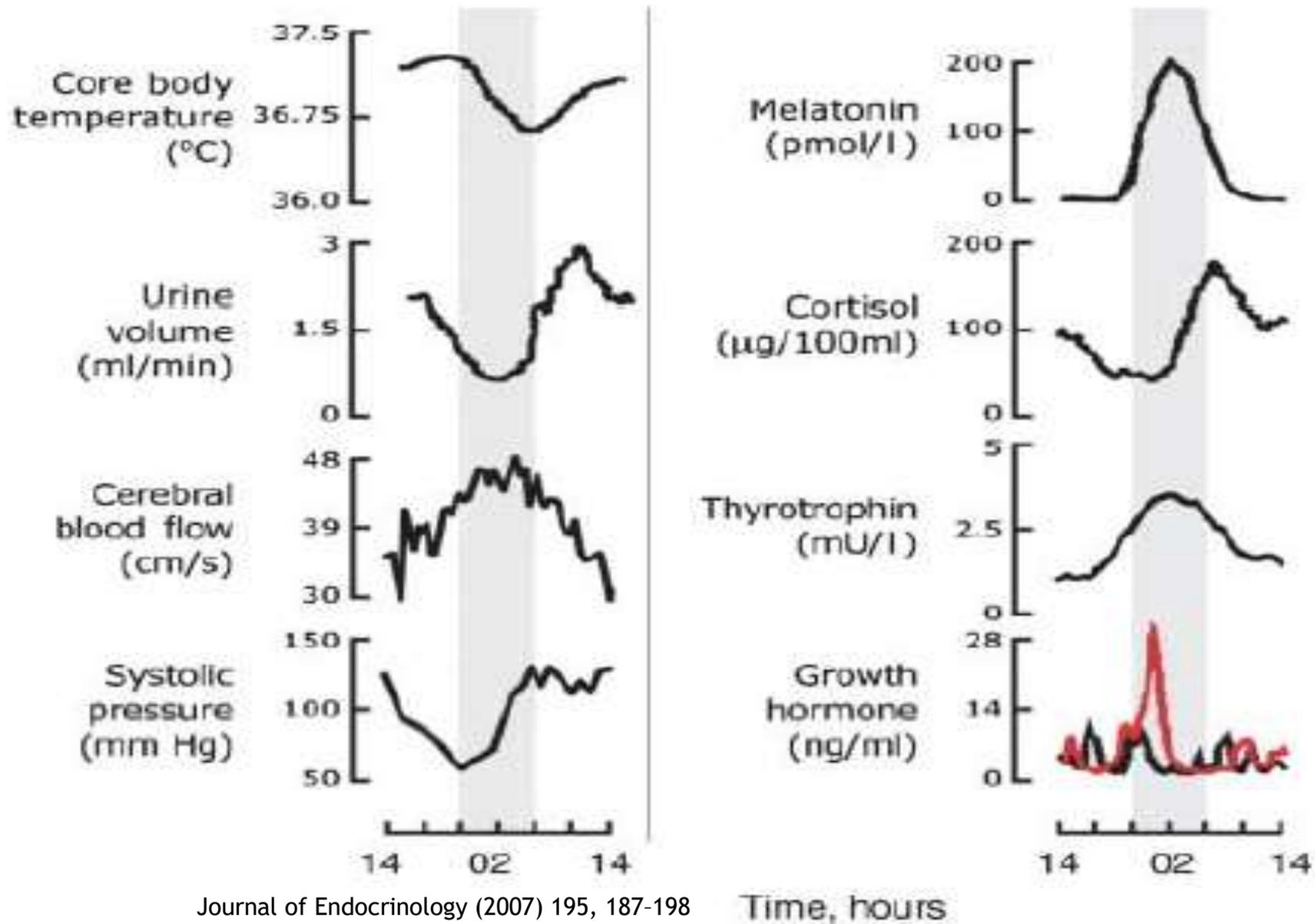
## **NIGHT**

**Relies on its body stores  
for long periods  
Stationary and hibernial  
Limited digestive system  
Carbohydrates may be  
harmful  
Slow metabolic rate**

# What are Circadian Rhythms?

~24-hour oscillations in physiology and metabolism that allow organisms to predict the availability of food and light





# 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%)



# Diurnal Rhythms of Cortisol in Women with PCOS

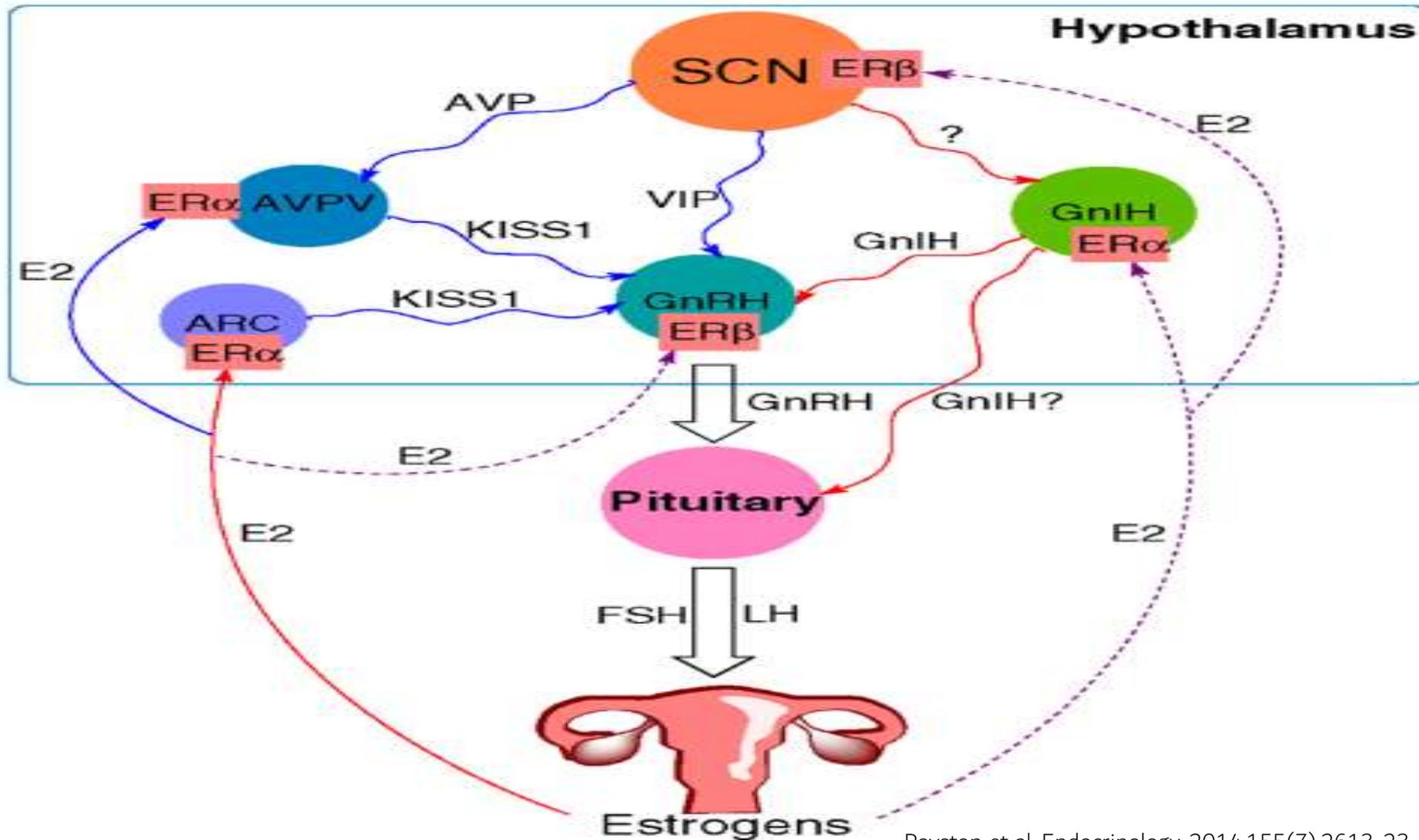


Morning: plasma cortisol is low among obese women with polycystic ovary syndrome

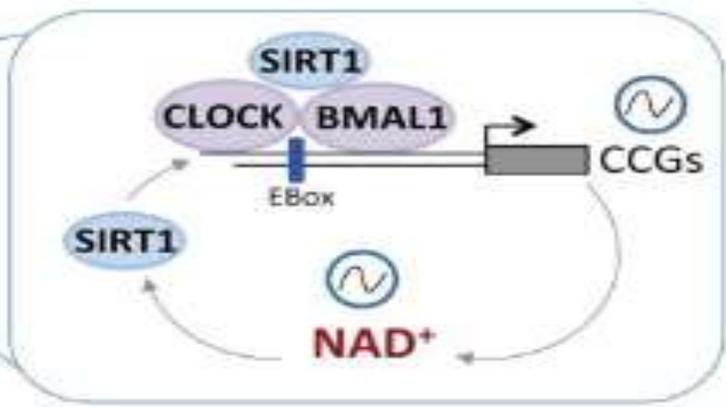


Evening: plasma cortisol level is higher in women with PCOS in study of 90 women

# Estrogen – Reproduction - Metabolism



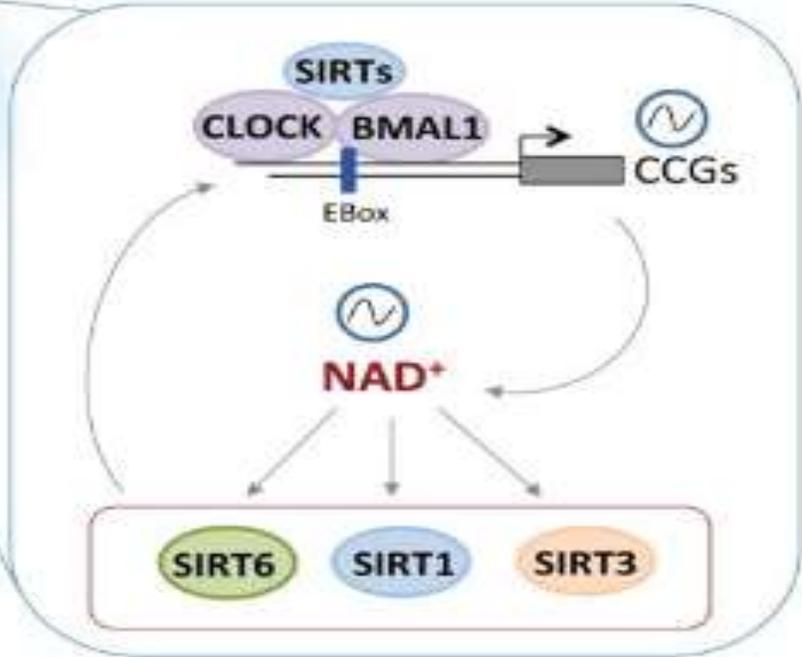
Regulation of the Circadian Clock in the brain



Regulation of the Hepatic Circadian Clock



Roles of other sirtuins?



**Sirtuin-dependent control of the circadian clock in the brain and periphery**

Masri et al. *Curr Opin Clin Nutr Metab Care* 2015.;18:521-527

# Peripheral Clocks: Present in Nearly Every Cell

- Regulate all biological functions - directly or indirectly
- Easily disrupted by improper food timing, regardless of light
- Adipose, Pancreas function impacted by erratic time of food consumption



Brain clocks



Vascular clocks



Liver clocks



Bone clocks



Ovarian

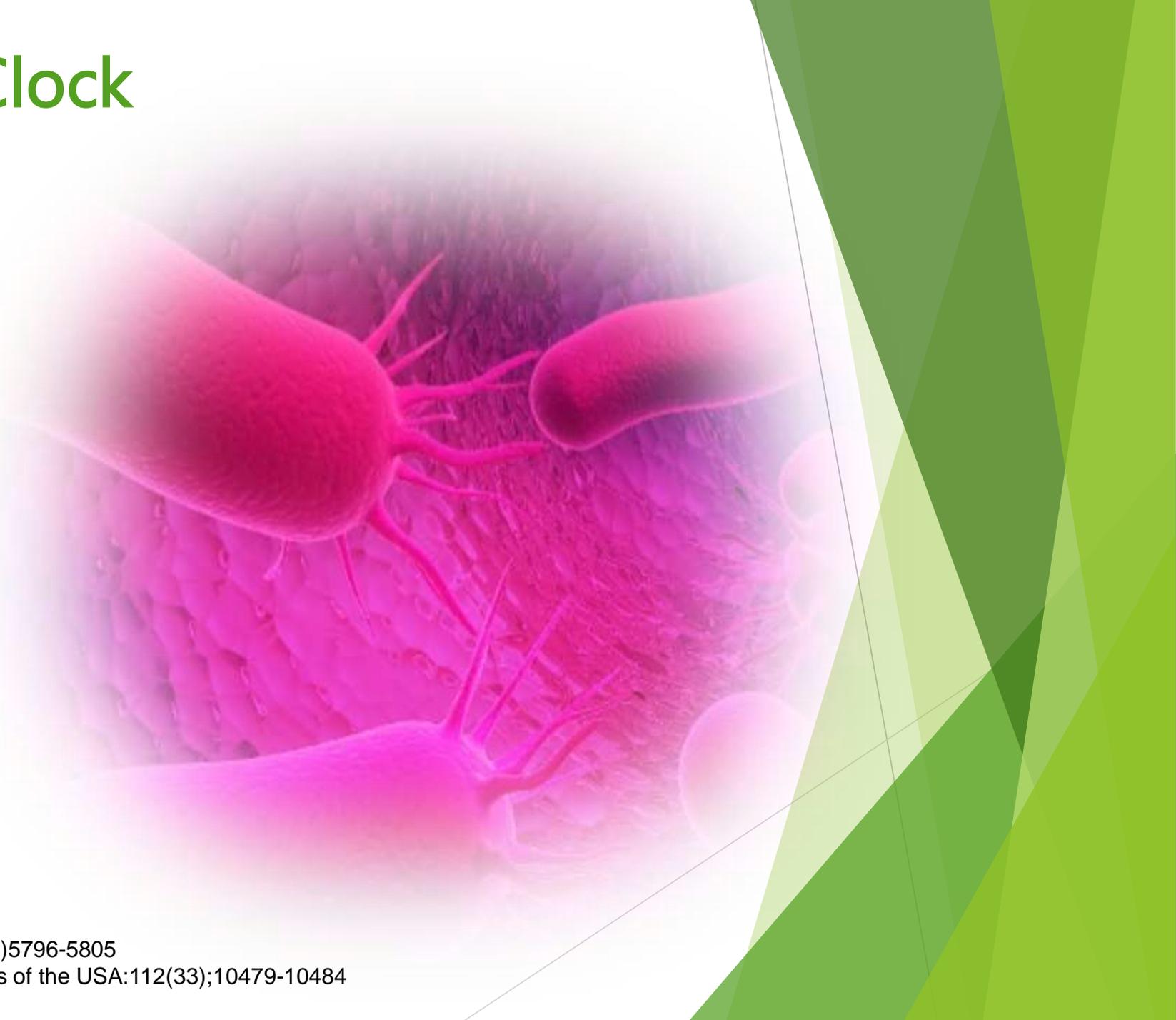


Gut clocks

# Gut Microbiome Clock

**Programmed to  
anticipate food in  
the daytime only**

**Bacteria express  
circadian patterns  
of swarming &  
motility**



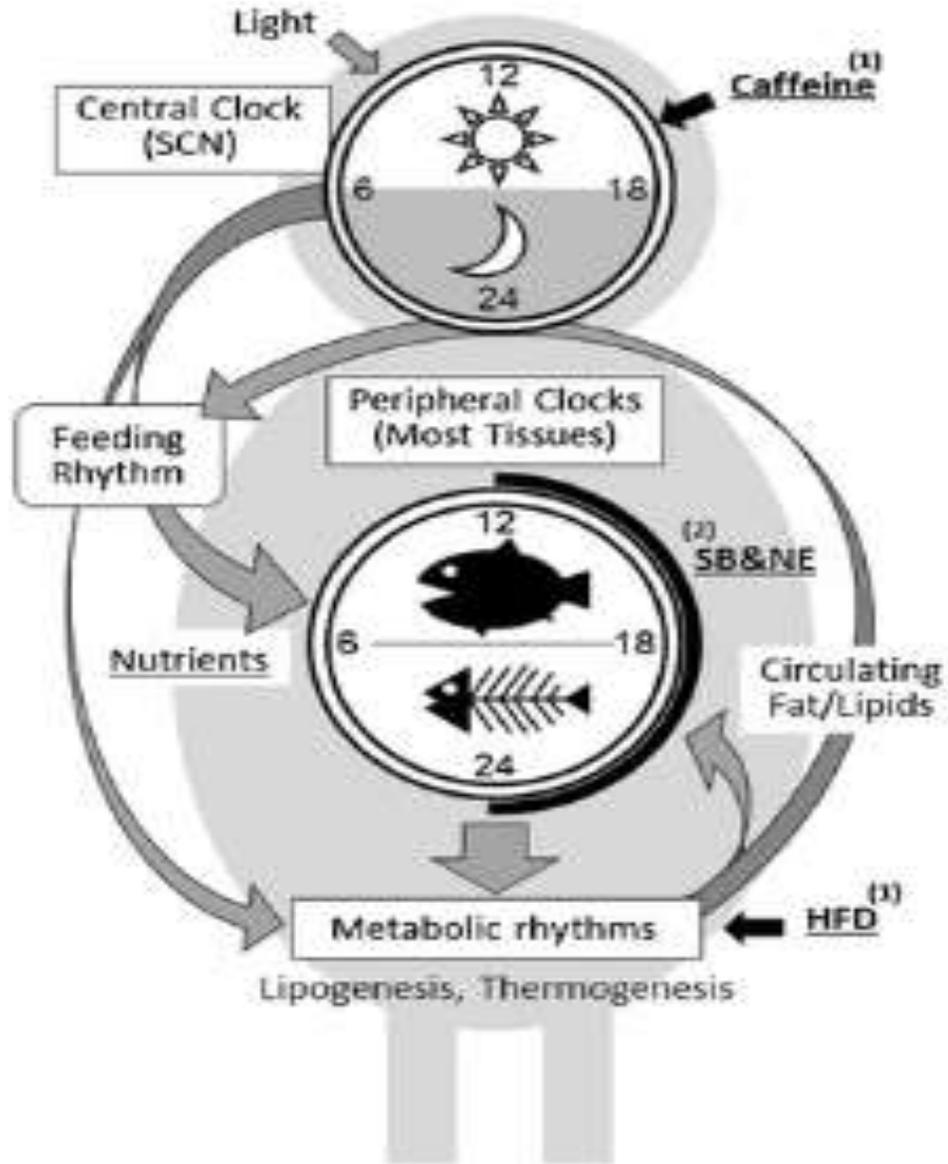
Marquie et al. *Occup Environ Med.* 2015;72(4):258-64

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

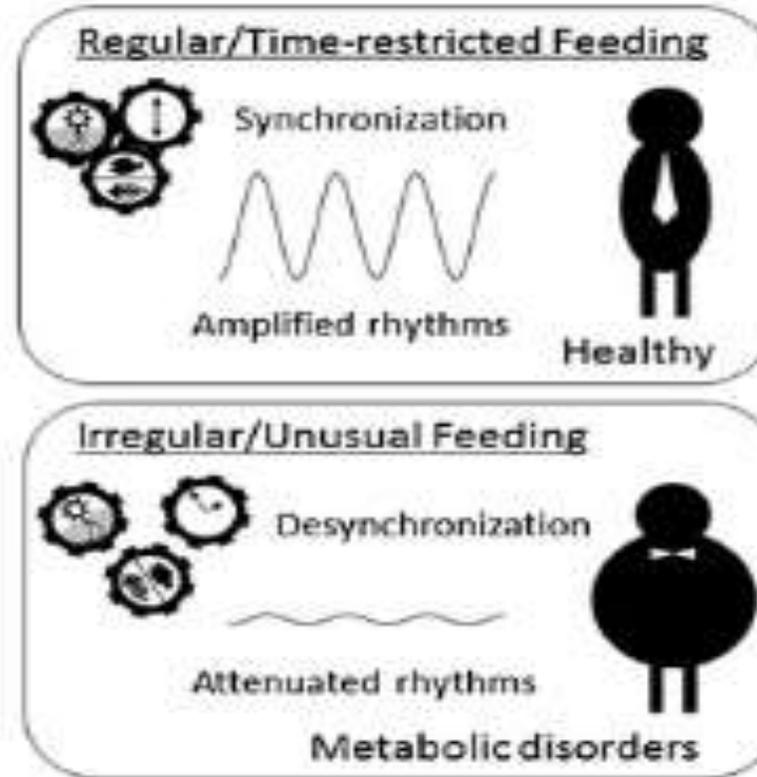
Bechtold et al. 2010; *Trends in Phar Scie*, 31(5):191-8

# Circadian Rhythm + Intestinal Epithelium



## Chrono-nutrition

- (1) Clock regulation  
ex. High-fat diet (HFD), Caffeine
- (2) Meal-time effects  
ex. Skipping breakfast (SB)  
Nocturnal eating (NE)



# My Integrative Approach *to Balance Hormones and Restore Health*

**Fitness**

**Gynecology**

**Nutrition**

**+ targeted supplements**

Lifestyle Educator  
Fitness Trainer  
Skin Care  
Stress Reduction/Meditation/Guided  
Imagery  
Therapeutic Massage/Aromatherapy  
Vascular Ultrasounds

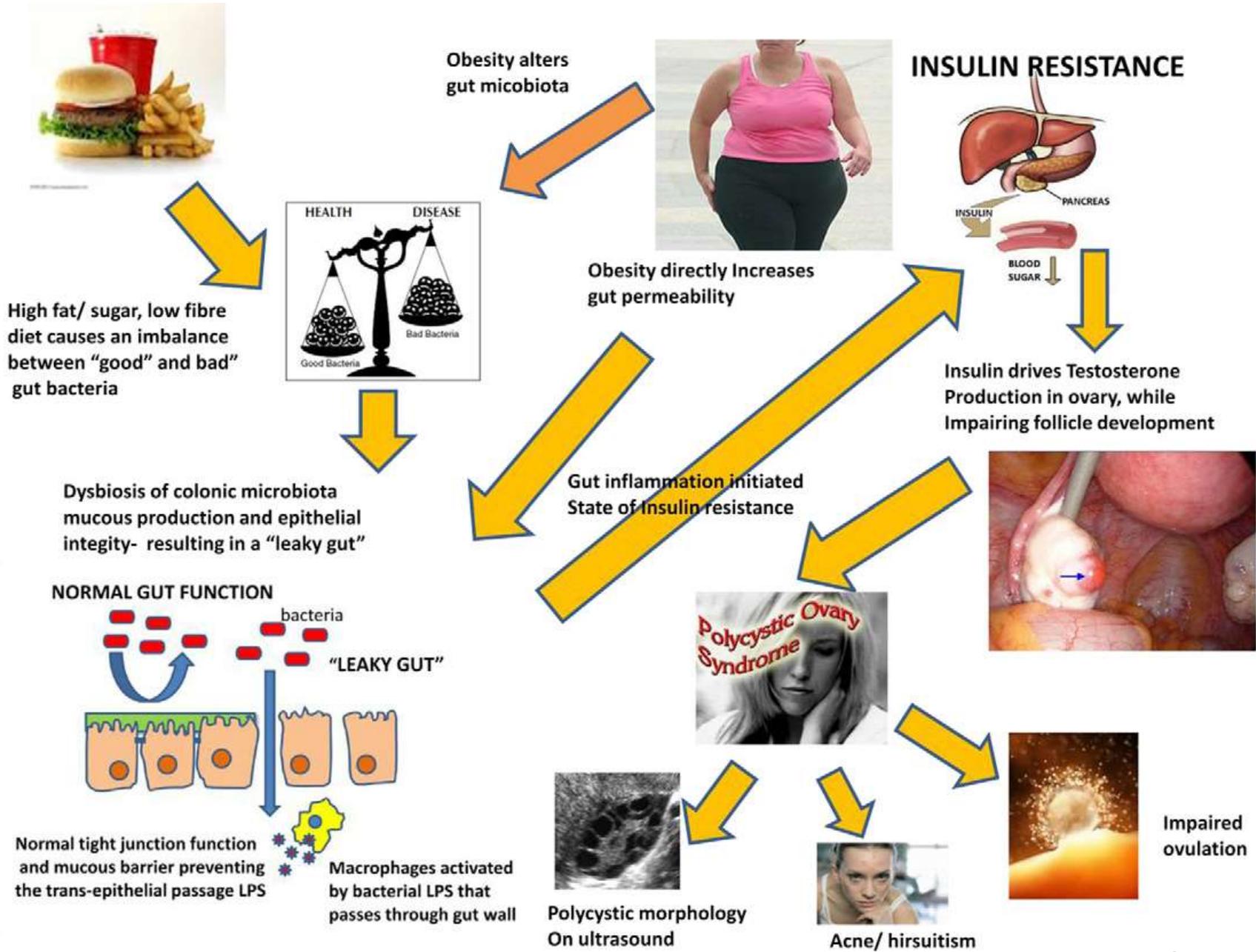
# My Integrative 7 Step Program

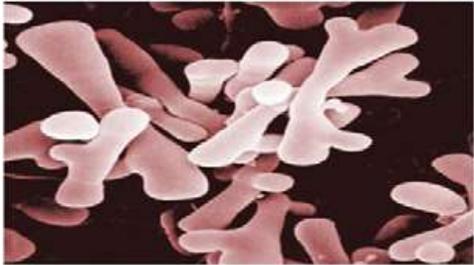


# 7 Steps to Optimizing Health for Women: Improving Metabolic and Reproductive Health

1. FEED THE GUT AND PRESCRIBE 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





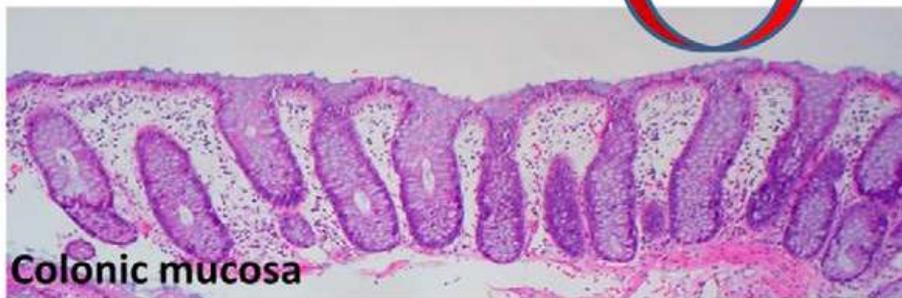


Probiotics and/or prebiotic treatment increases the number of beneficial "good" bacteria in the colon



Beneficial "good" bacteria produce Short Chain Fatty Acids (SCFA) that increase colonic mucous production and tight junction function- decreasing the passage of immuno-stimulatory LPS from the colonic lumen into the circulation

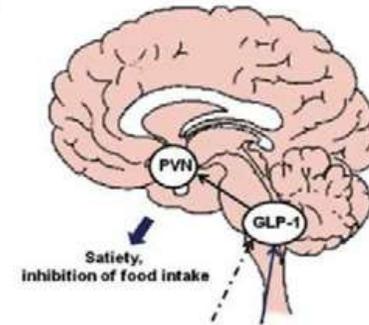
**Bacterial LPS**



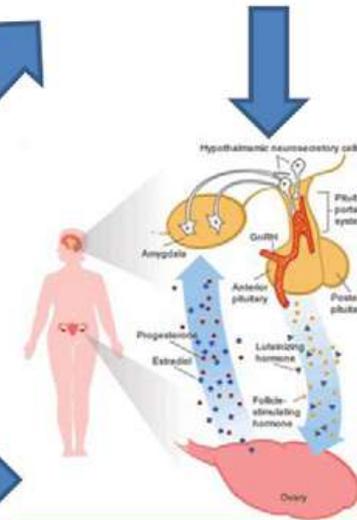
Colonic mucosa



A reduction in inflammation due to reduced passage of LPS across the gut mucosa results in an improvement in insulin sensitivity, with a drop in serum insulin levels

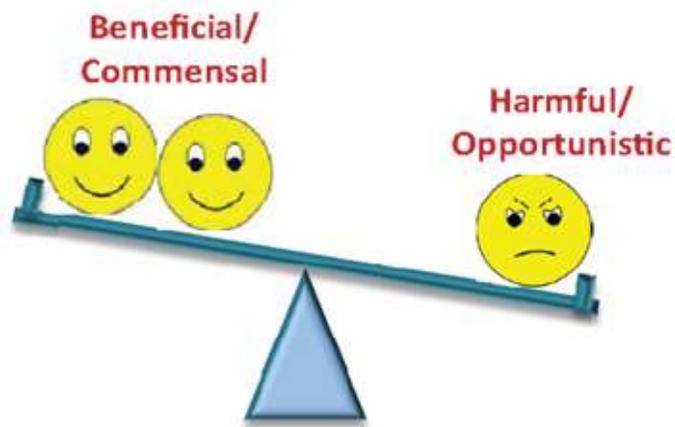


Increased production of the satiety hormone GLP-1 by the healthy colon mucosa reduces food intake and results in a Decrease in body fat content



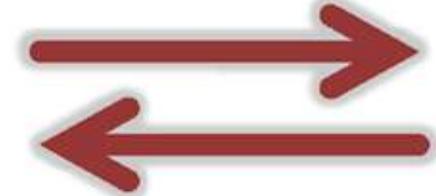
**RETURN TO NORMAL OVARIAN FUNCTION**

# Work to Achieve a Healthy Gut Microbiome

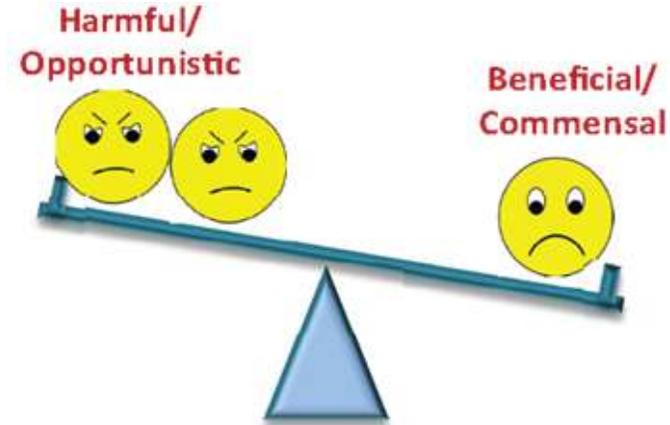


**Balanced gut microbiota**

High-fat/ high-sugar diets,  
over-nutrition, sedentary  
lifestyle, antibiotic abuse



Prudent diet & lifestyle,  
probiotics/ prebiotics,  
Anti-inflammatory/  
immune-potentiating  
therapeutics, nutraceuticals



**Gut microbial dysbiosis**

↓Gut permeability;  
↓Toxemia/Sepsis;  
↓Proinflammation;  
↑Insulin sensitivity;  
↑gut/metabolic/cardiovascular  
health

↑Gut permeability;  
↑Endotoxemia; septicemia;  
↑Systemic inflammation;  
↑Insulin resistance;  
↑Adiposity, diabetes, MetS,  
CVD, NAFLD, NASH, IBD, IBS etc.

“Importance of balanced nutrition and gut microbiota, and consequences of gut dysbiosis. MetS, metabolic syndrome; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; IBD, inflammatory bowel disease; IBS, irritable bowel syndrome; CVD, cardiovascular diseases.”

# Feed the Gut

- Eat mostly plants
  - Eat lots of fiber
  - Eat organic, raw, minimally processed foods – spanning the colors of the rainbow
  - Limit sugar, fat, salt
  - Avoid alcohol, antibiotics from agriculture, artificial sweeteners, dairy, emulsifiers, gluten
  - Recommend targeted supplements
  - Reboot – eat vegan for 6 months
  - Get some great cookbooks, aligned with the plan
-

# Complex Carbohydrates (70% of diet)



# Best Diet to Nourish the Microbiome

## EXTREMELY HIGH FIBER

|                |   |
|----------------|---|
| <b>INCLUDE</b> | <ul style="list-style-type: none"><li>▶ Complex carbohydrates (70%) whole-grains, all varieties of vegetables, beans, legumes, etc.</li><li>▶ Healthy fats from nuts, seeds, olives<br/>Add Omega 3 supplement</li><li>▶ Natural fiber and prebiotic rich foods</li><li>▶ Probiotic rich foods</li><li>▶ Green leafy vegetables and root vegetables</li></ul> |
| <b>LIMIT</b>   | <ul style="list-style-type: none"><li>• Protein (approximately 12%)</li></ul>   |
| <b>AVOID</b>   | <ul style="list-style-type: none"><li>• Initially, no protein from animals, dairy, or eggs</li><li>• NO Sugar and refined carbohydrates</li><li>• NO Alcohol</li><li>• AVOID ANY Food intolerances</li></ul>  |



# Targeted Supplements for Metabolic Support

DIM

Vitamin D

Curcumin

Magnesium

Probiotic

Omega 3

Prenatal  
Vitamin

Myo-  
inositol

NAC

Berberine

Chaste  
Tree

Zinc

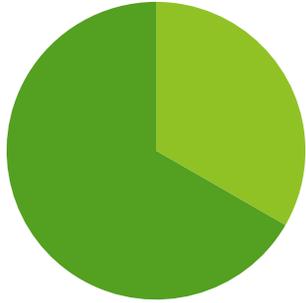
# Eat to the Beat

|             |  |
|-------------|--|
| <b>Eat</b>  | <b>during the day</b>                                      |
| <b>Eat</b>  | <b>big breakfast,<br/>moderate lunch, small<br/>dinner</b> |
| <b>Eat</b>  | <b>dessert with breakfast</b>                              |
| <b>Eat</b>  | <b>meals, not snacks</b>                                   |
| <b>Fast</b> | <b>at night</b>  |



### Typical American Meal Pattern

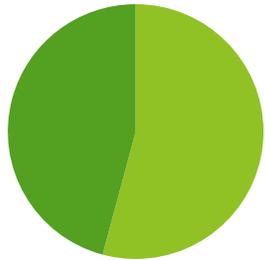
16 hour  
daytime  
eating  
period



8 hour  
overnight  
fast

### Circadian-Aligned Meal Pattern (A)

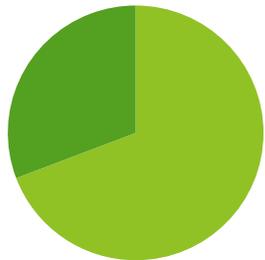
11 hour  
daytime  
eating  
period



13 hour  
overnight  
fast

### Circadian-Aligned Meal Pattern (B)

8 hour  
daytime  
eating  
period



16 hour  
overnight  
fast

# Correct the Clock: Meal Timing

**Eat dinner early**

**Eat same times daily**

**Limit snacking**

**Eat breakfast to dinner 13  
hours apart**

**Eat a large, healthy  
breakfast by 10 AM**

*Incorporate fasting  
mimicking diet or periodic  
water fast*

# Correct the Clock: Meal Timing Matters

## Israeli Study:

High caloric intake at breakfast & reduced intake at dinner

### Significant changes:

- ▶ **Glucose – decreased 7 %**
- ▶ **Insulin – decreased 54%**
- ▶ **Testosterone – decreased 50%**
- ▶ **SHBG – increased 105%**
- ▶ **17 OH progesterone – decreased 39%**
- ▶ **Increased ovulation rate**

# See the Light

“Watch” the  
sunrise

Morning light

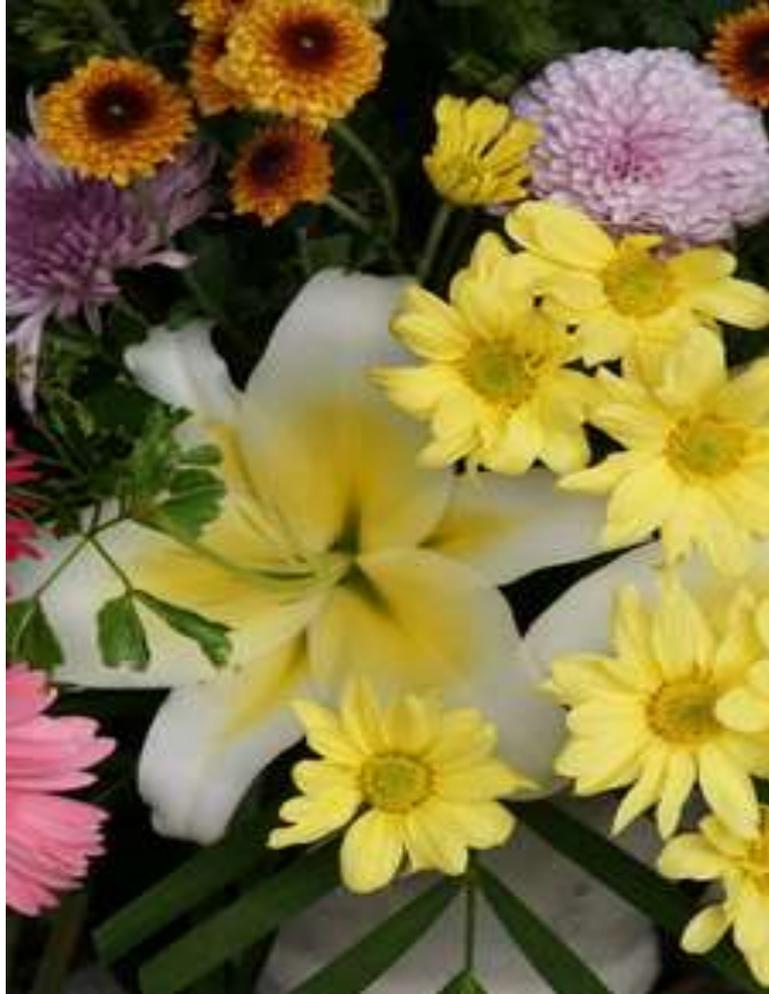
Midday sun

Watch the  
sunset

Dim the lights  
- reduce blue  
light exposure

Sleep in the  
dark

Go camping



# Get Enough Sleep

**Set up**

**a sleep routine and stick with it**

**Make**

**the bedroom a wonderful place to sleep**

**Consider**

**supplements to lower stress and support sleep**

**Get**

**a relaxation routine - start 2 hours before bedtime**

**Limit**

**caffeine to mornings**

**Test and treat**

**sleep apnea**

**Attend**

**to heartburn and any other painful condition**



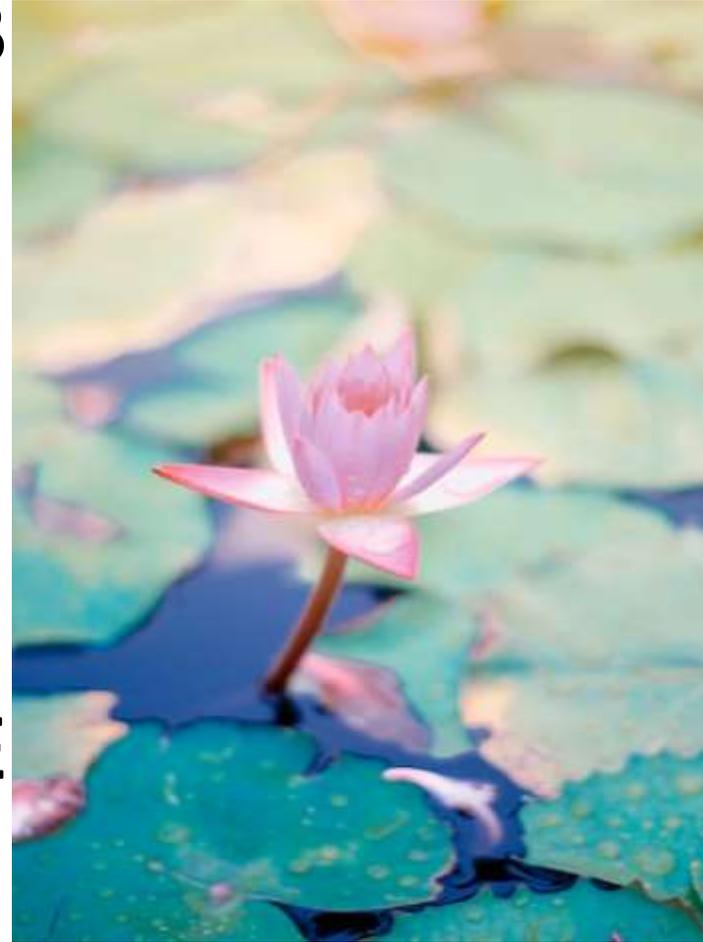
# Exercise Every Chance You Get

|              |   |
|--------------|---|
| <b>Move</b>  | <b>every day</b>                                    |
| <b>Take</b>  | <b>a walk after meals</b>                           |
| <b>Do</b>    | <b>something fun and strenuous 3 times per week</b> |
| <b>Focus</b> | <b>on functional fitness</b>                        |
| <b>Time</b>  | <b>workouts to fitness goals</b>                    |



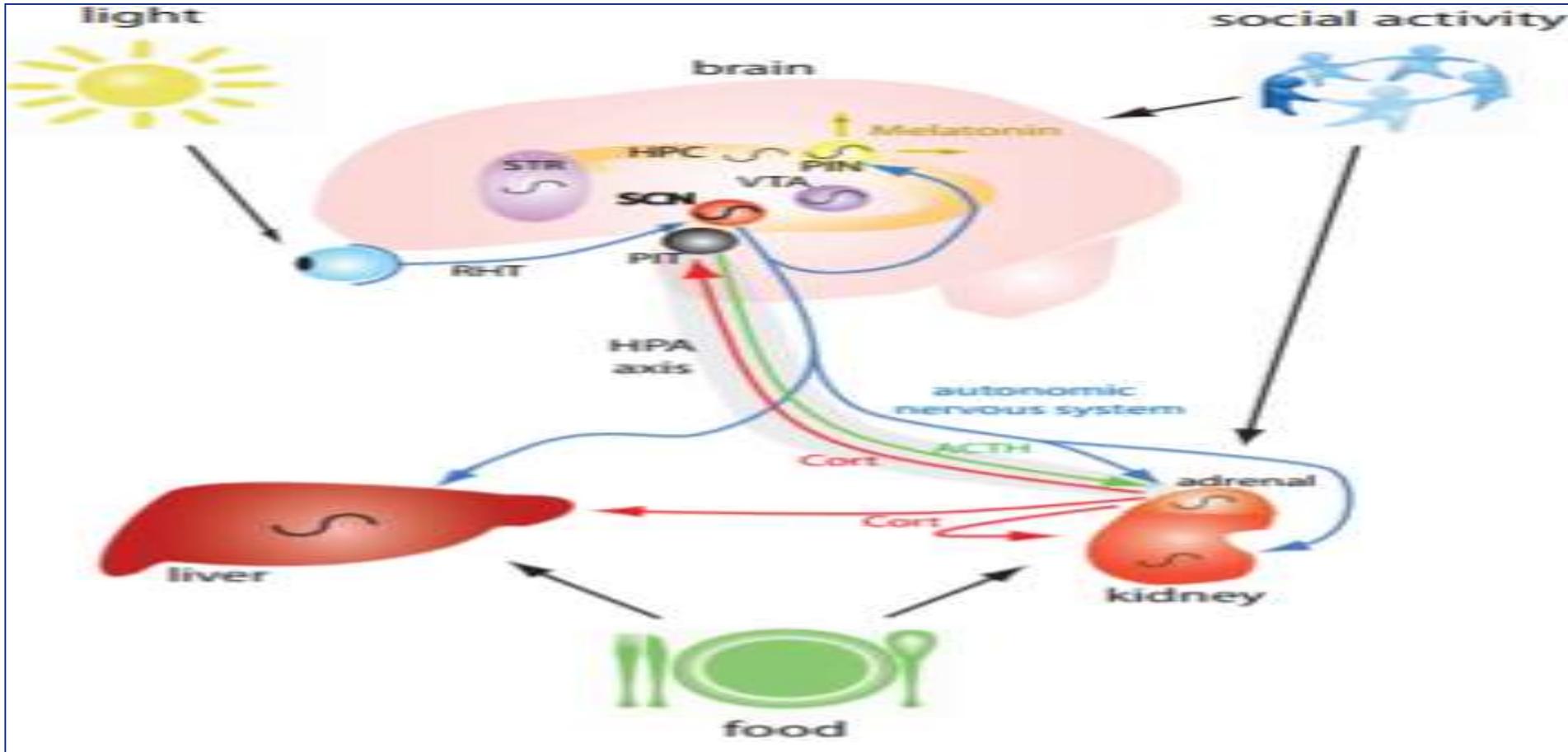
# Help Your Patients Stick with the Plan: Metabolic & Reproductive Health can be Achieved

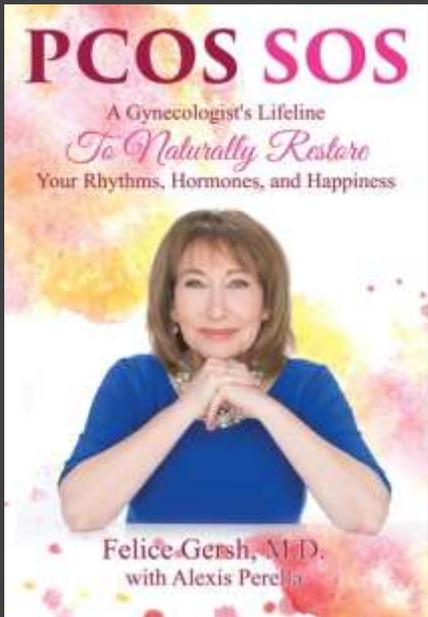
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# Path to Hormonal Health

## Metabolic Health – Fertility Optimization





*Thank you!*

Felice L. Gersh, MD

- [www.integrativemgi.com](http://www.integrativemgi.com)
- Twitter: @DrFeliceGersh
- Instagram: Dr.FeliceGersh
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