OVERCOMING POLYCYSTIC OVARY SYNDROME:

Addressing the Complex Roles of Endocrine Disruptors, the Gut Microbiome, and the Circadian Rhythm

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Learning Objectives

1. Review the fundamentals of Polycystic Ovary Syndrome (PCOS) – the leading cause of female infertility
2. Analyze the interplay between metabolic and reproductive health, and how PCOS embodies difficulties with both components, impacting overall female health
3. Recognize the role of estrogen and its receptors on the manifestations of PCOS
4. Compare and summarize the critical roles played by the gut microbiome and the circadian rhythm in the myriad manifestations of PCOS
5. Develop an efficacious, holistic, and therapeutic approach to PCOS that incorporates the newest understandings of this condition

Women's Optimal Health = Optimized Hormones

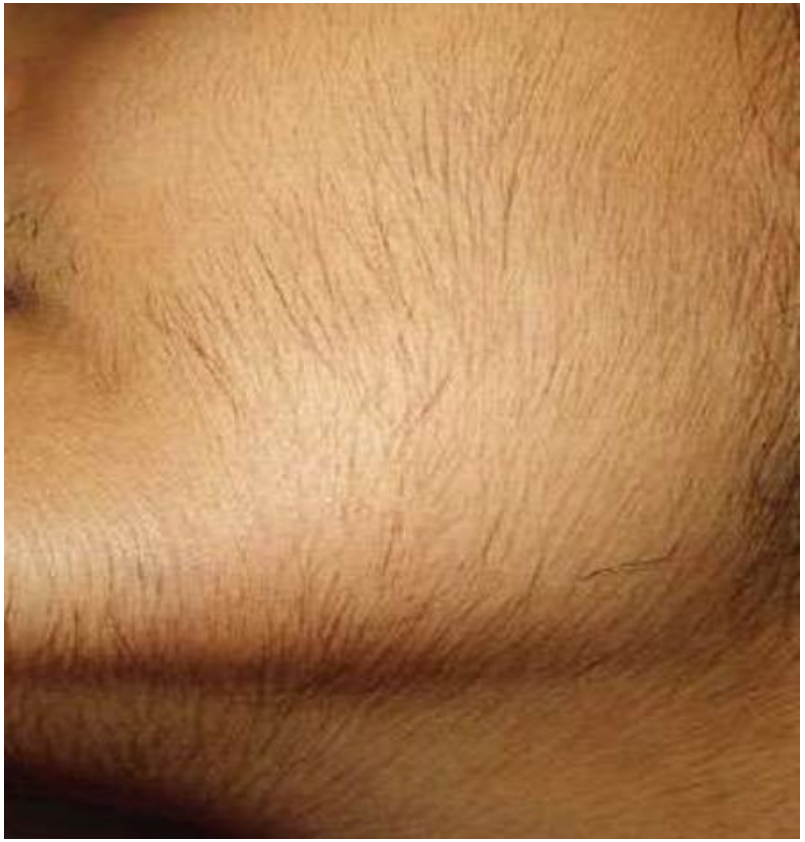
Prime Directive of Life:

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

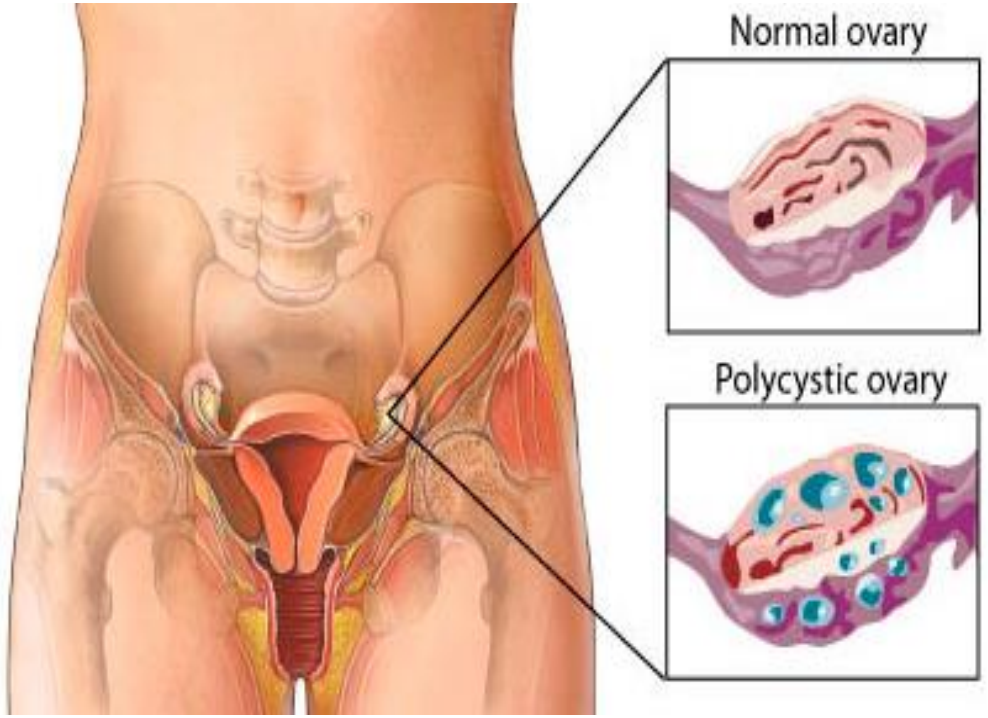
- Acne
- Hirsutism
- Alopecia
- Irregular cycles
- Obesity
- Fatigue
- Joint pains
- Gingivitis
- Depression
- IBS

What's Changed?

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

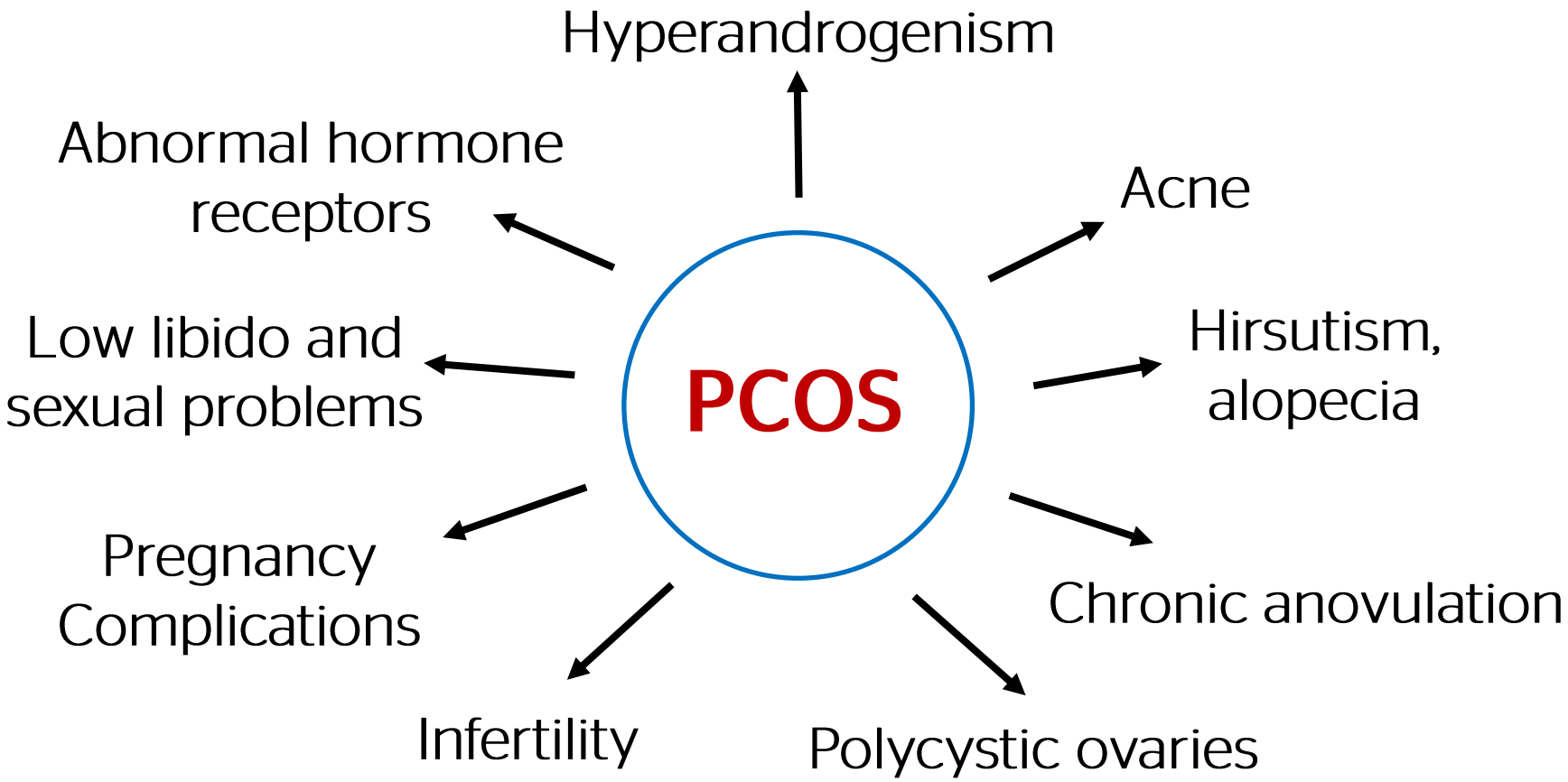
Polycystic Ovary Syndrome (PCOS) Uniting Everything in a Woman: Hormones, Circadian Rhythm, Environmental Toxicants, and Cardio-metabolic Health

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

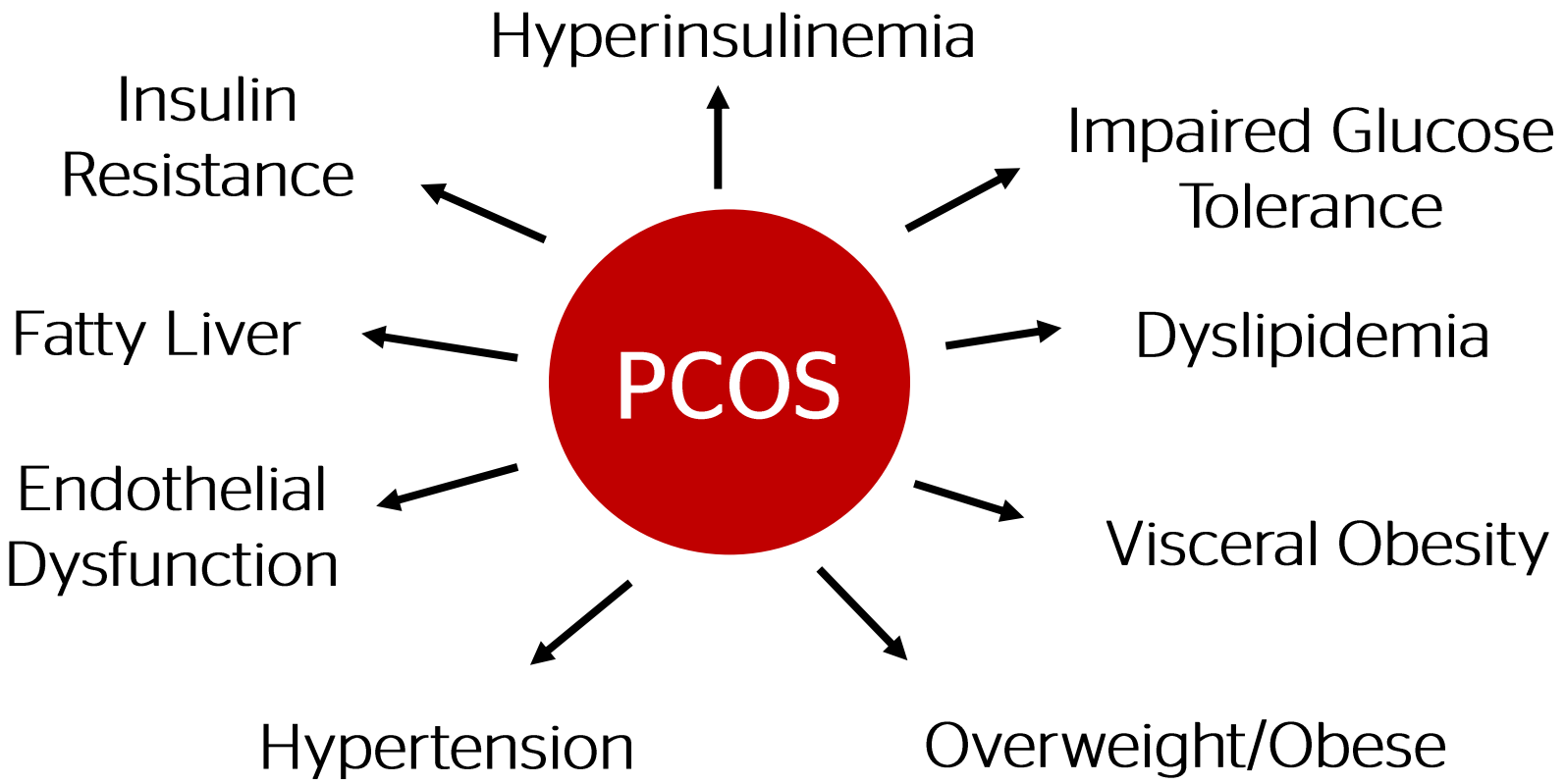


https://www.womenshealth.gov/publications/our-publications/fact-sheet/images/pcos1.jpg

Hormonal/Reproductive Effects of PCOS



Metabolic Effects of PCOS



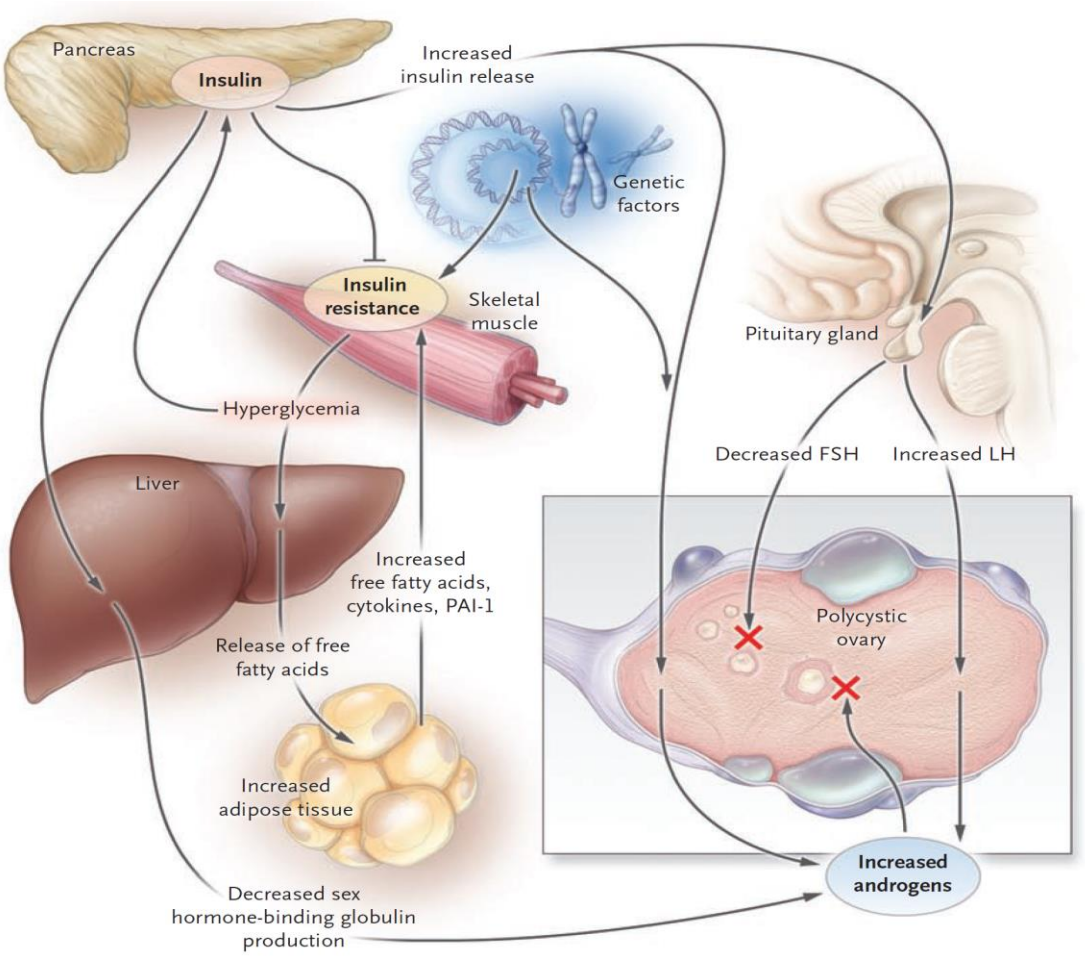
Use of fasting blood to assess the prevalence of insulin resistance in women with polycystic ovary syndrome. (2004) Fertil. Steril
Prevalence and predictors of dyslipidemia in women with polycystic ovary syndrome. (2001) Am. J. Med.

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 and Metabolism

Dysregulation of various hormonal and metabolic processes



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

Etiology of PCOS

Complex interaction between genetics and the environment

Prenatal risk factors:

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

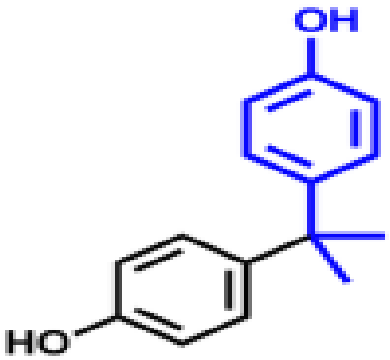
Adult exacerbation with:

- Hormonal imbalances
- Chronic inflammation
- Metabolic dysfunction
- GI imbalances

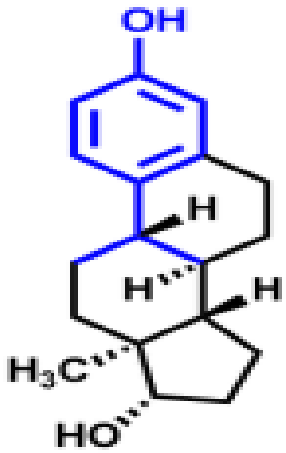
Nestler JE. N Engl J Med. 2008; 358: 47-54

Endocrine Disruptors

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



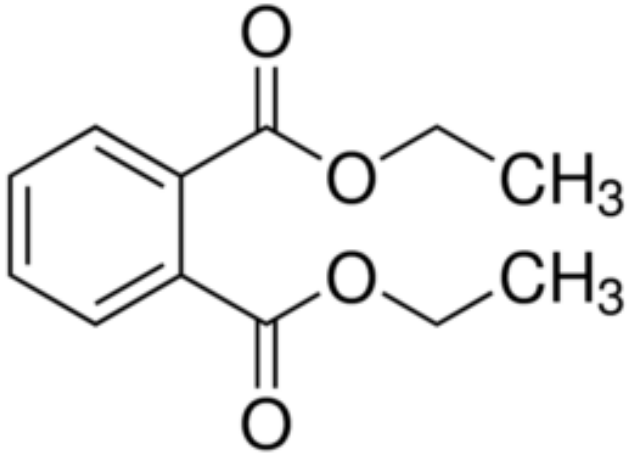
Bisphenol-A (BPA)



Estradiol

Known Endocrine Disruptors

- Phthalates
- Alkylphenolic compounds
- Polychlorinated bisphenols
- Polychlorinated dibenzodioxins
- Organochlorine pesticides
- Bisphenol A
- Lead
- Mercury
- Cadmium



Phthalate

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

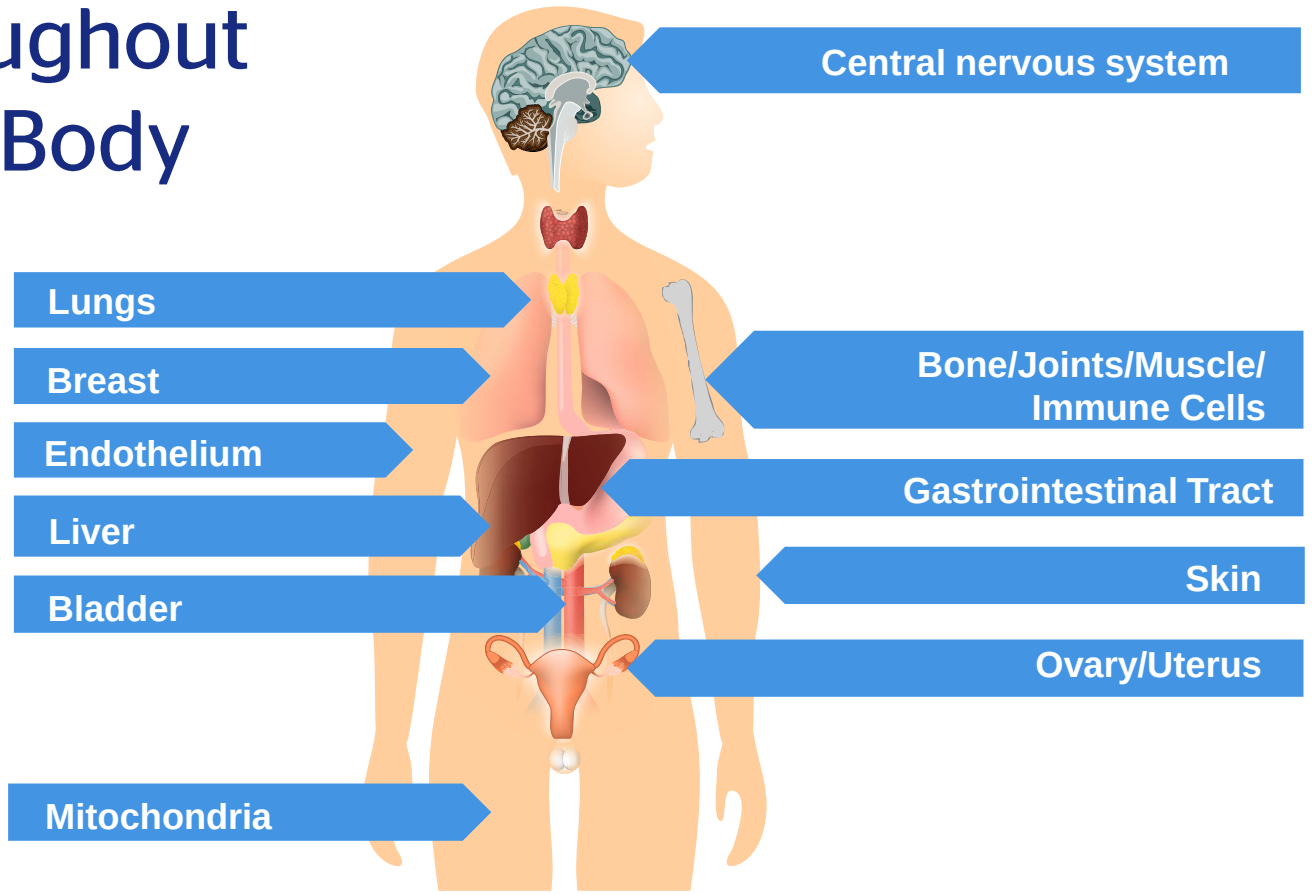
Artimani et al. Gynecol Endocrinol. 2015

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!

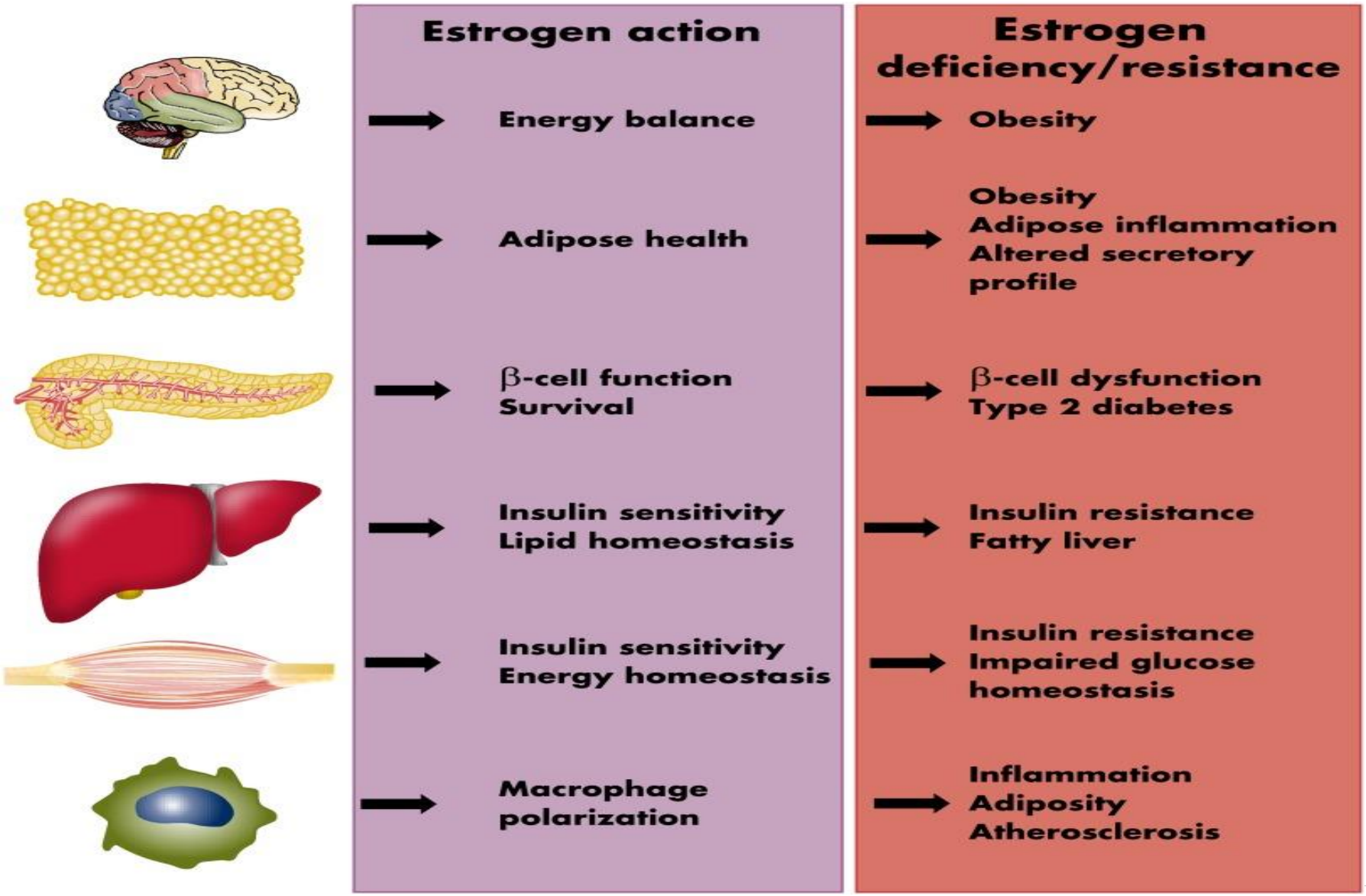
Lateef A and Petri M. J of Autoimm. 2012; 38: J170-J176.

Klein S and Flanagan K. Nat Rev Immunol. 2016 Oct16(10):626-38..

Consequences of Estrogen Deficiency

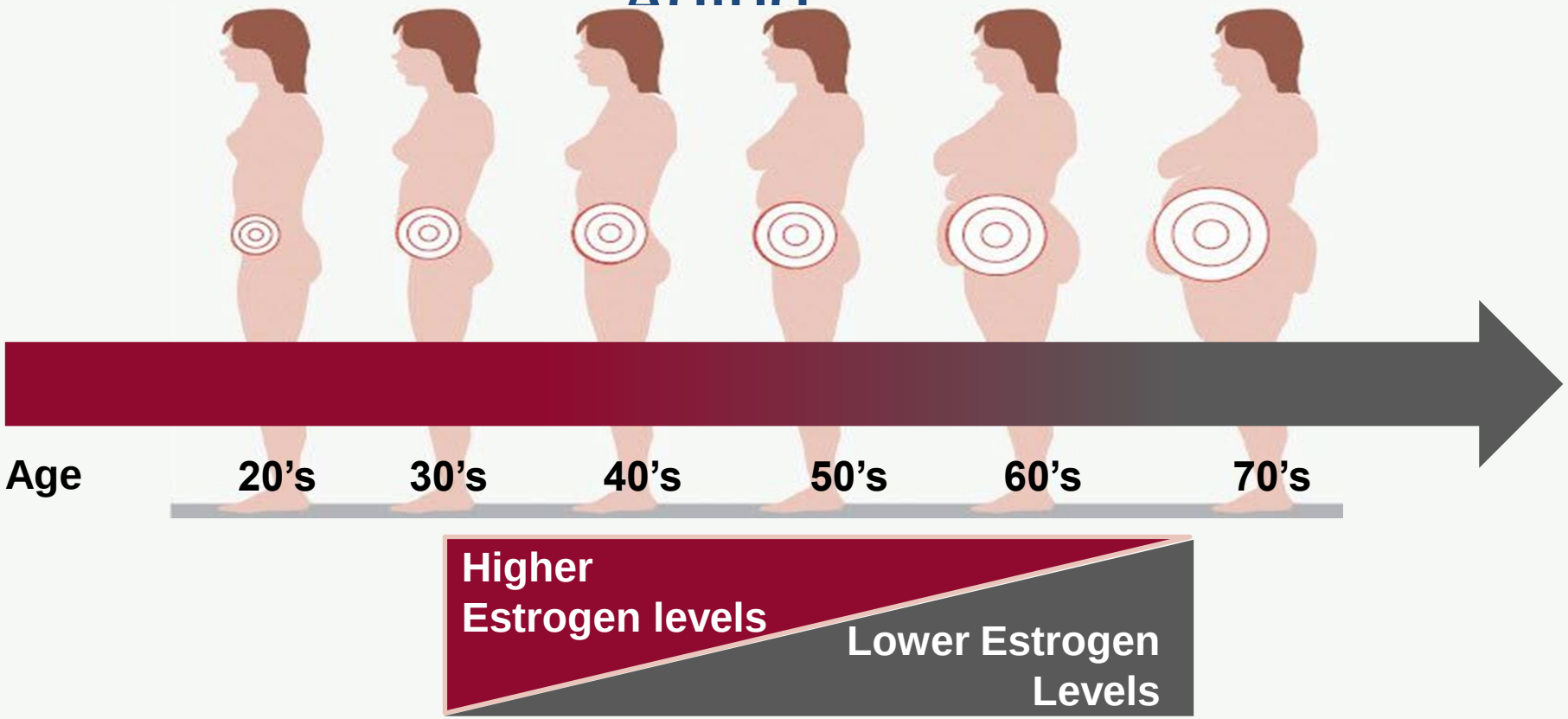
- Obesity
- Disturbed Sleep
- Mood Disorders
- Metabolic Syndrome and Diabetes
- Fatty Liver
- GI Disorders: Colon Cancer, GERD, Malabsorption
- Cardiovascular Health and Atherosclerosis
- Osteoporosis
- Alzheimer's Disease and Neuro-inflammatory Dx
- Breast Cancer

Adapted *from Exper Rev Endocrinol Metab* ® 2011 Expert Reviews Ltd



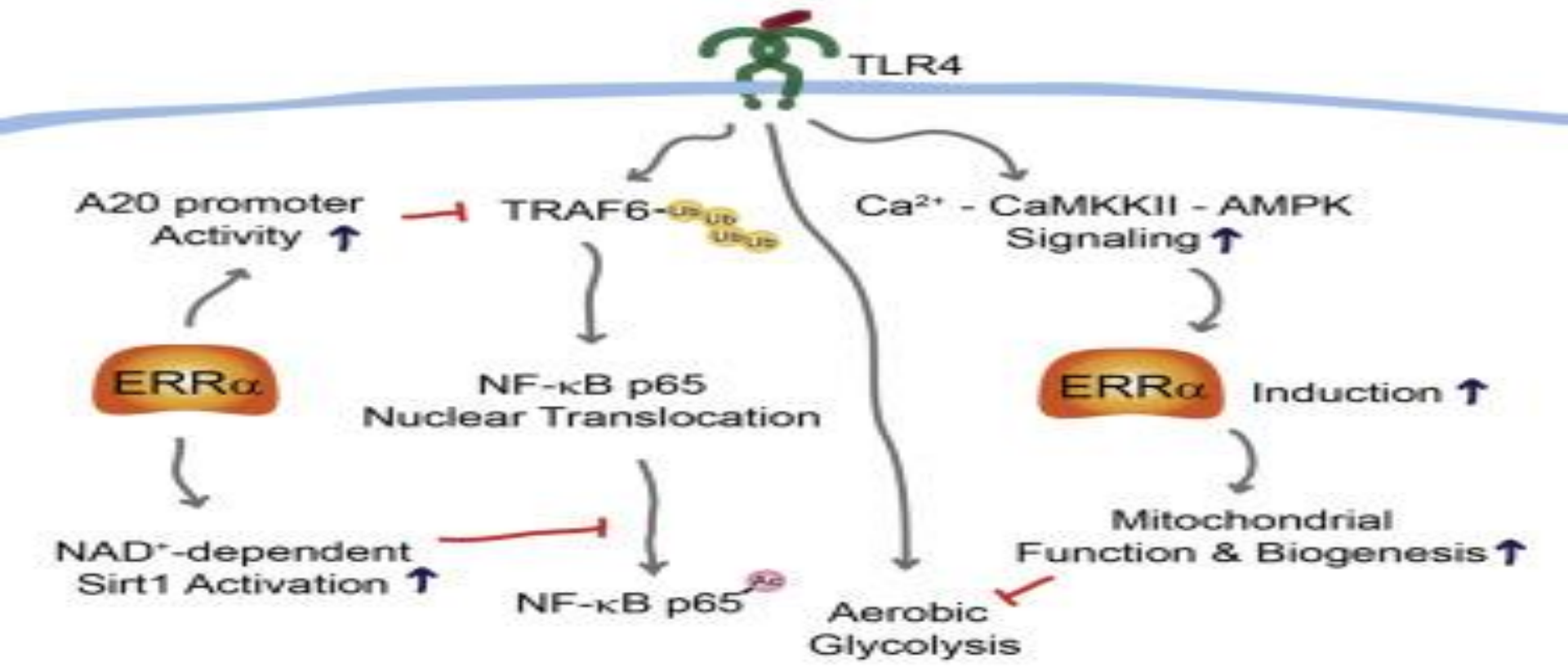
Mol Cell Endocrinol. Evolution of steroid receptors from an estrogen-sensitive ancestral receptor 2011;334:31-38
Endocr Rev The role of estrogens in control of energy balance and glucose homeostasis 2013; 34 (3): 309-338

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



Adapted *from Exper Rev Endocrinol Metab* ® 2011 Expert Reviews Ltd

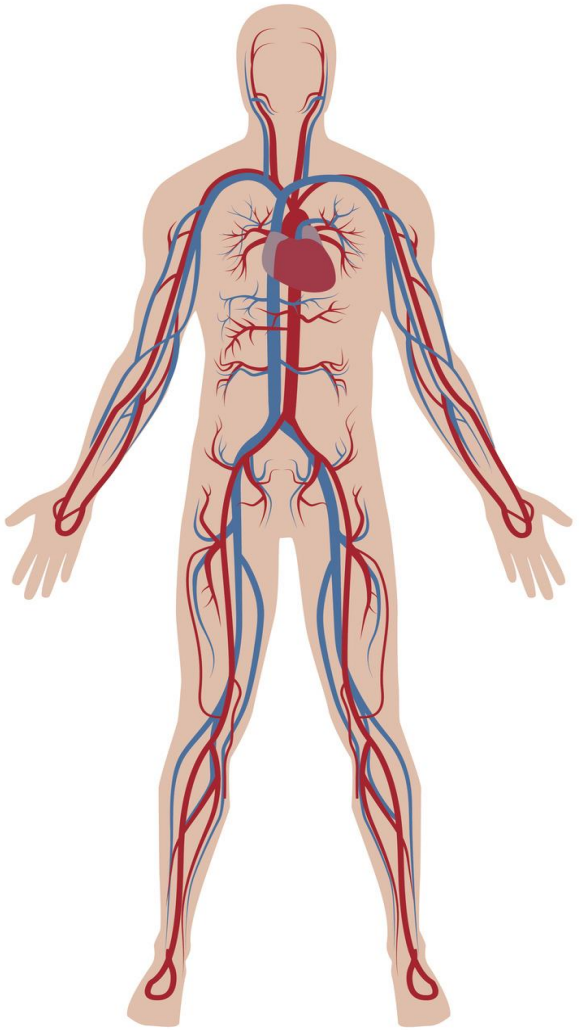
Estrogen Maintains NAD levels and Activates SIRT1 to Reduce Inflammation



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

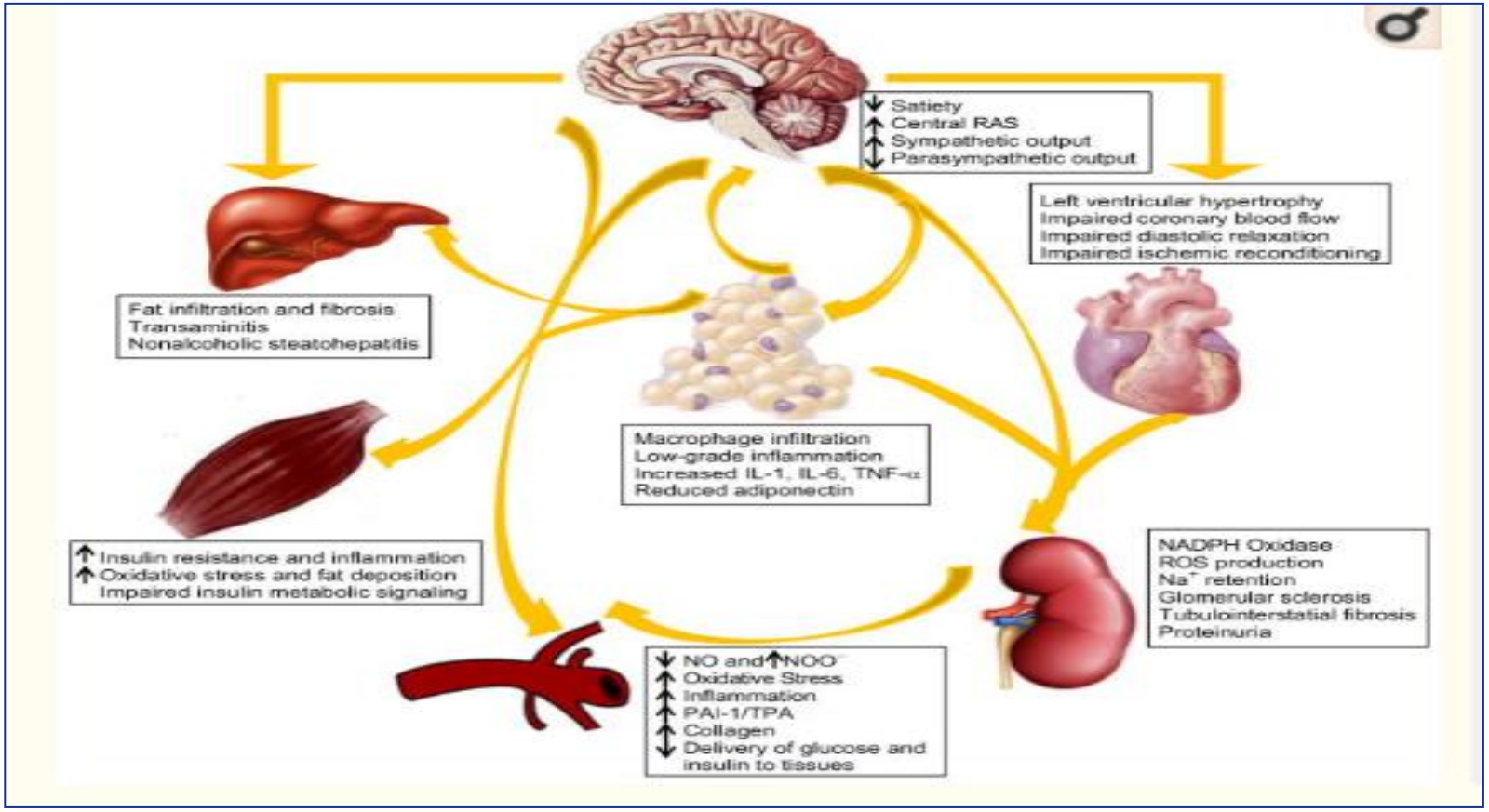
Nitric Oxide is Reduced in PCOS

- 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

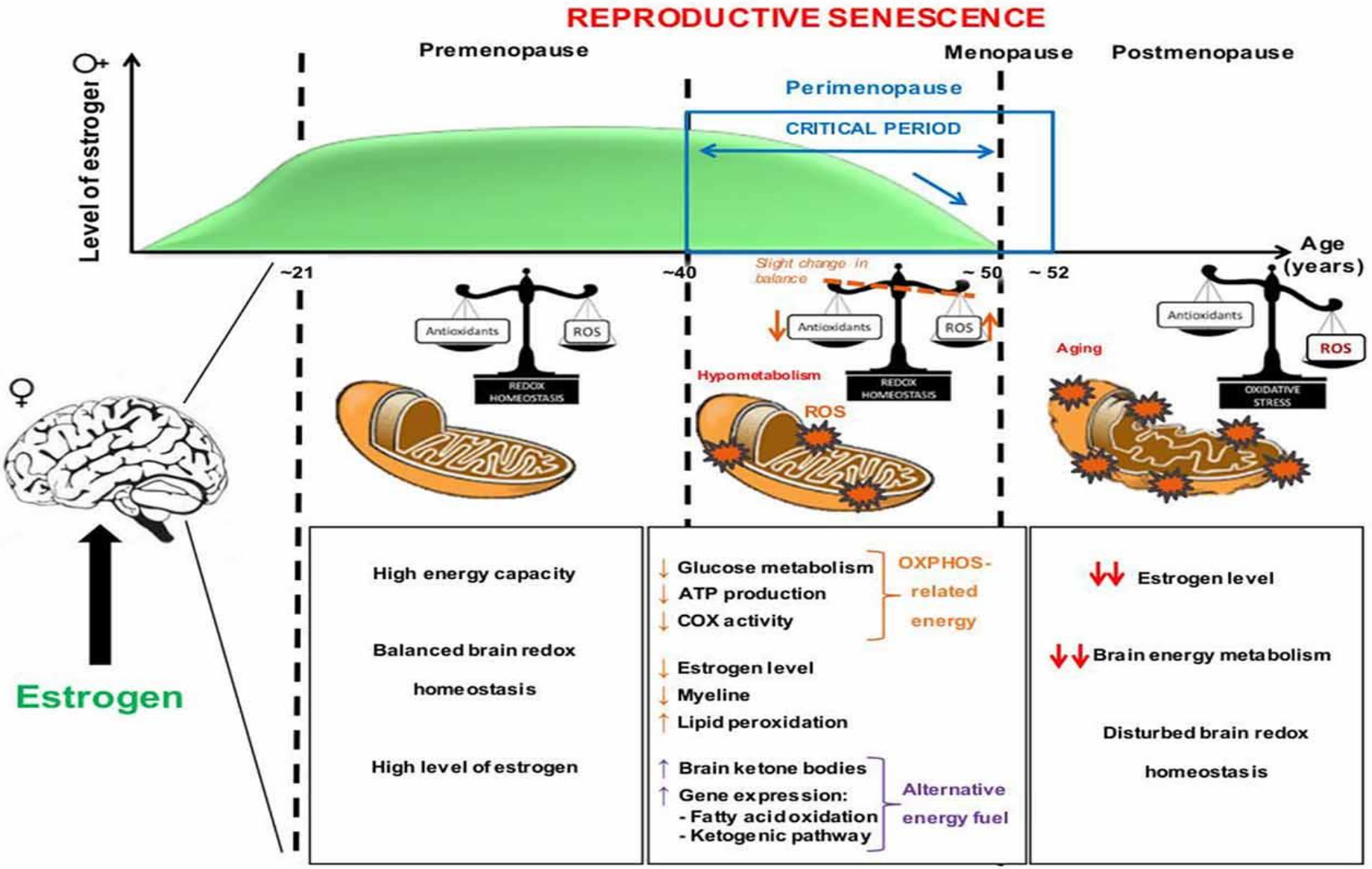


Krishna et al. Cell Physiol Biochem. 2017; 43:1880-1892

Cardio-Renal-Vascular-Metabolic Syndrome



Guanghong et al. Prog Mol Biol Transl Sci. 2014;127: 229-249



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

Inflammation: Driving Force of PCOS

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

The Gut Microbiome:
The Unseen Civilization Within Us

A Healthy Microbiome Supports all Systems

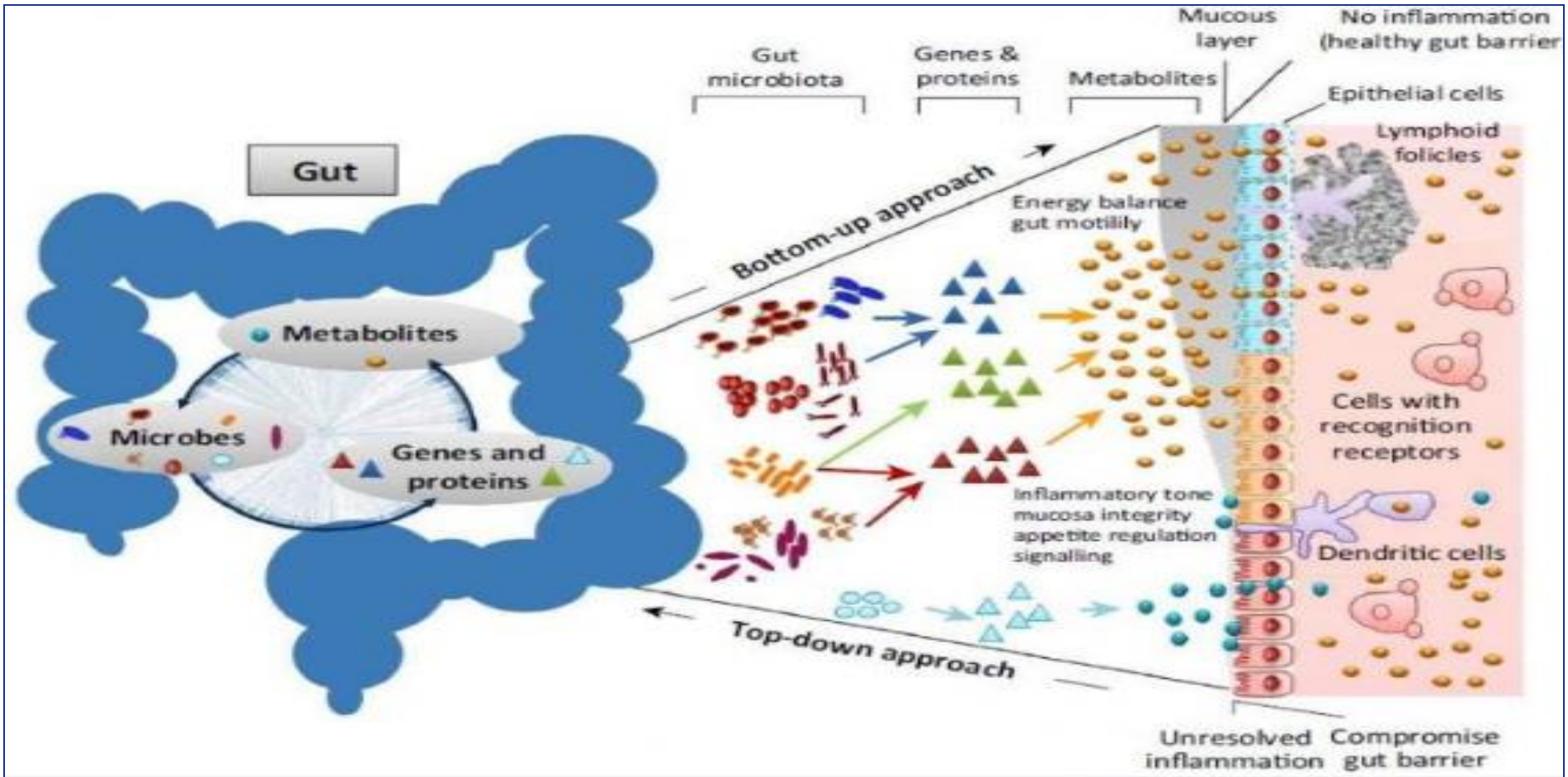
1. Immune activity
2. Hormone elimination
3. GI integrity
4. Metabolic health

PCOS Associated with Impaired Gut Function

- 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

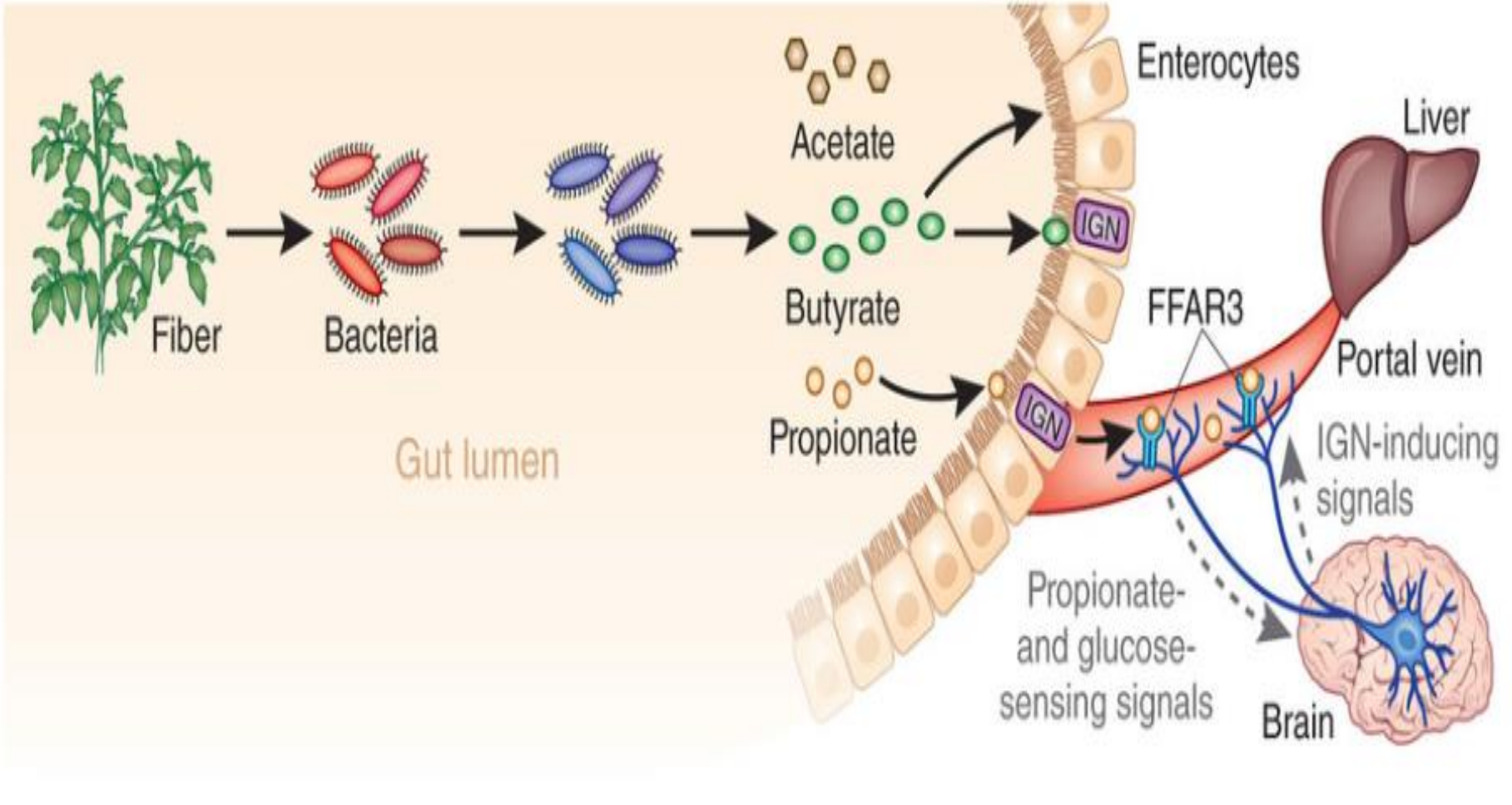
Lindheim et al; PLOS One. 2017.12(1)
Guo et al ; PLOS One. 2016
Liu et al. Font. Microbiol. 2017;8,324:1-12

Complex World of the Gut



This figure shows how microbiota species are interchangeable in terms of functions by means of the metabolites produced by the action of gene products contained in the gut bacteria.

Linking the Microbiome & Short Chain Fatty Acids to Metabolic Health



Nature Biotechnology. 2014; 32, 243–245

Poor diet + PCOS drive Dysbiosis

Dysbiosis → Systemic Inflammation

High fat/high sugar diet leads to Gut dysbiosis + *Circadian Rhythm dysfunction*

Guinane CM et al. Tole of the gut microbiota inhealth 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

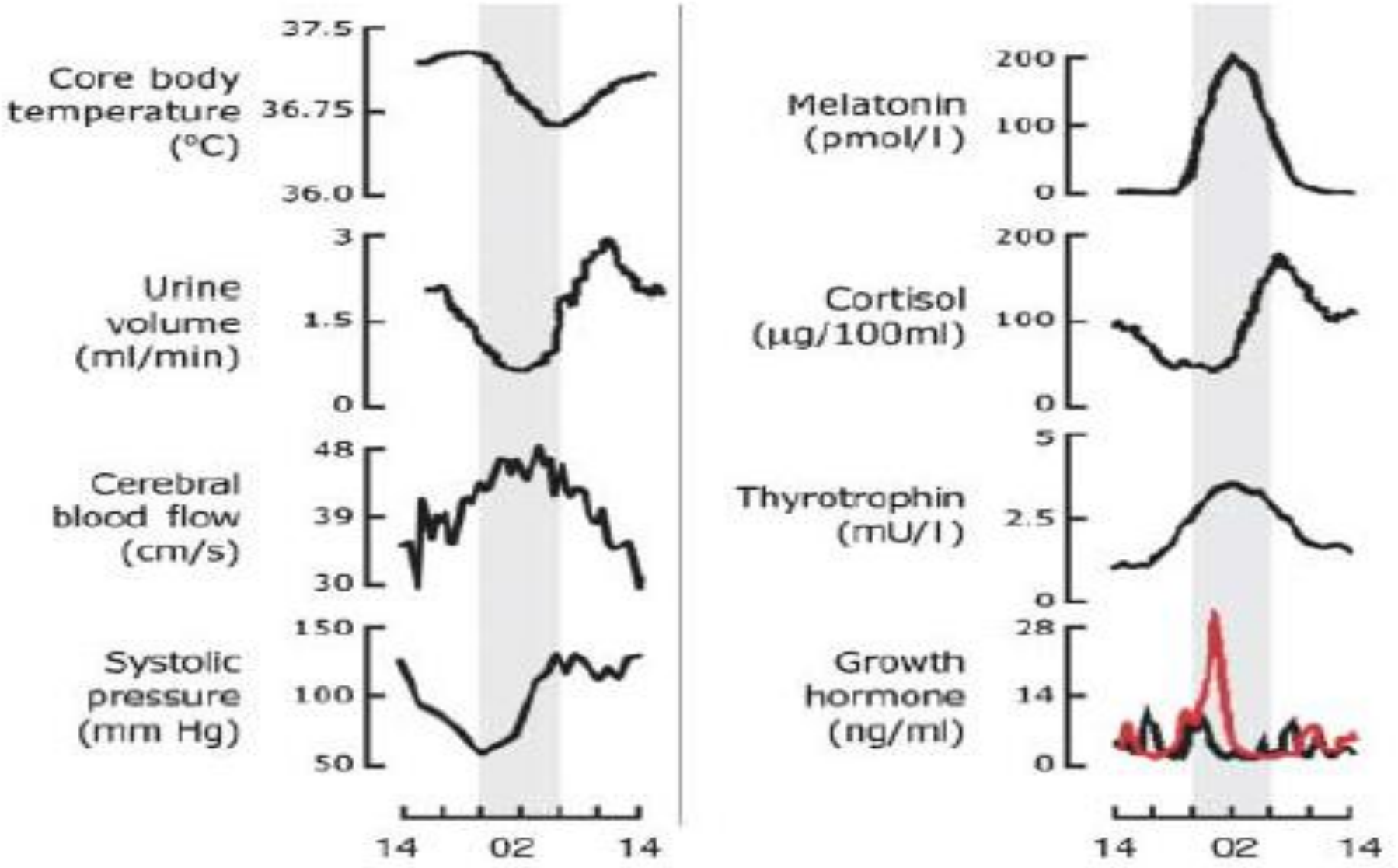
- Eats other organisms (plants, animals)
- Active and mobile
- Fully functional digestive system
- Prefers carbohydrates
- High metabolic rate

NIGHT

- Relies on its body stores for long periods
- Stationary and hibernal
- 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



Journal of Endocrinology (2007) 195, 187–198

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

Impaired Sleep Contributes to …

- Inflammation
- Insulin resistance
- Poor cardiometabolic health
- Poor mood

Fernandez RC, Moore VM, Van Ryswyk EM, et al. *Nat Sci Sleep.* 2018;10:45–64.

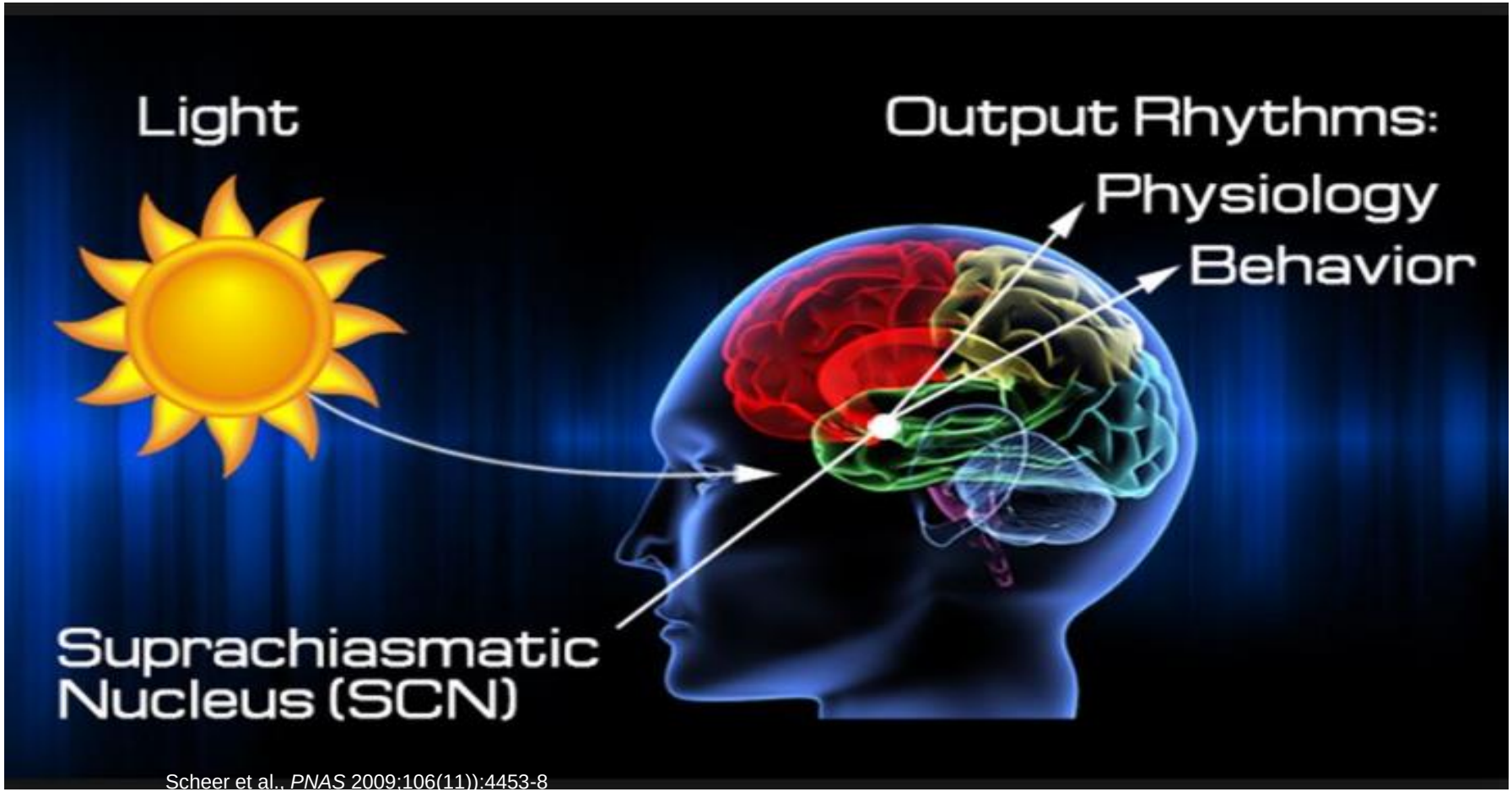
Diurnal Rhythms of Cortisol in Women with PCOS

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

Kialka et al. Przegl Lek. 2015;72(5):240-2
Shabir et al. Gynecol Endocrinol. 2013;29(12):1045-7

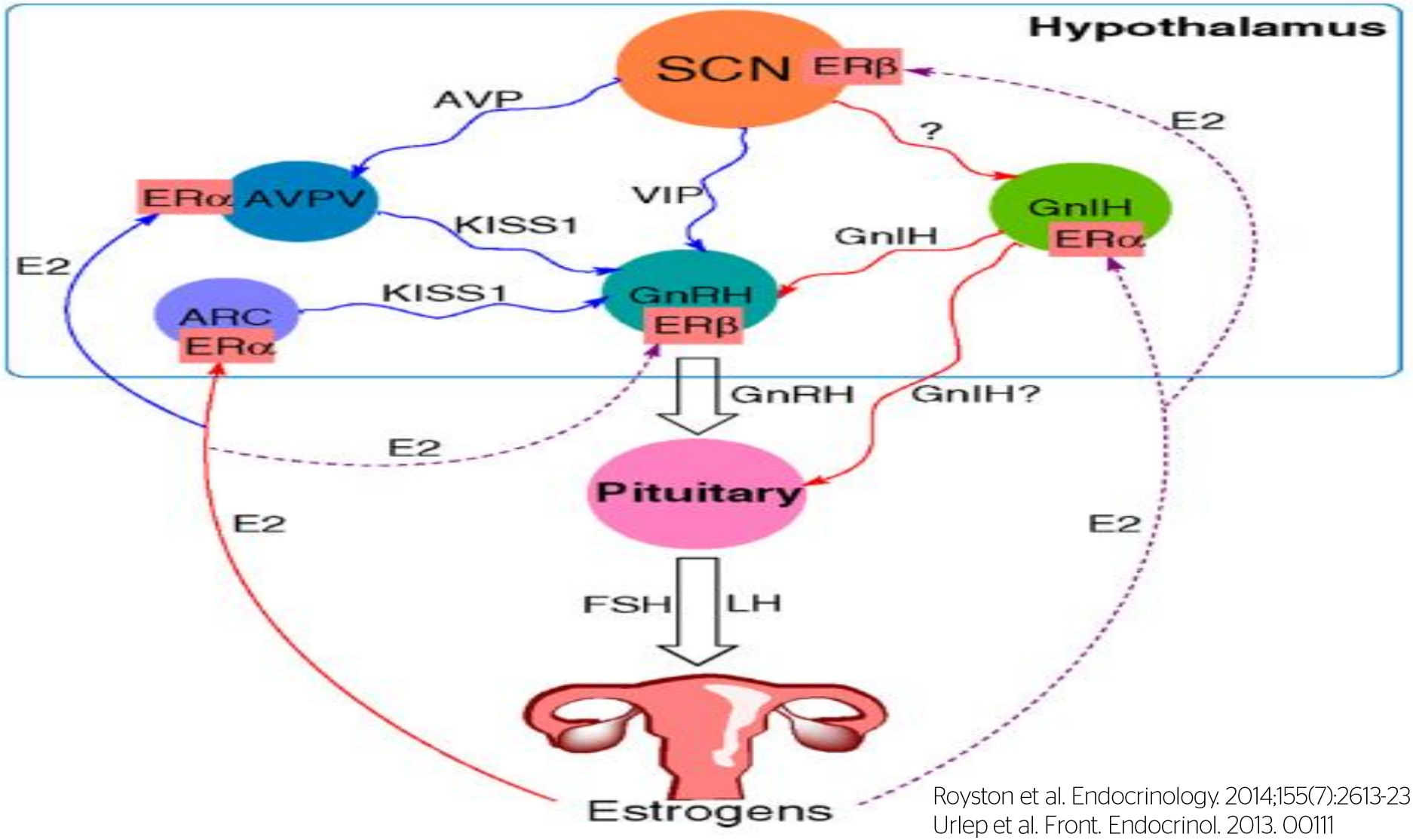
The Suprachiasmatic Nucleus: Keeping the Beat with Estrogen



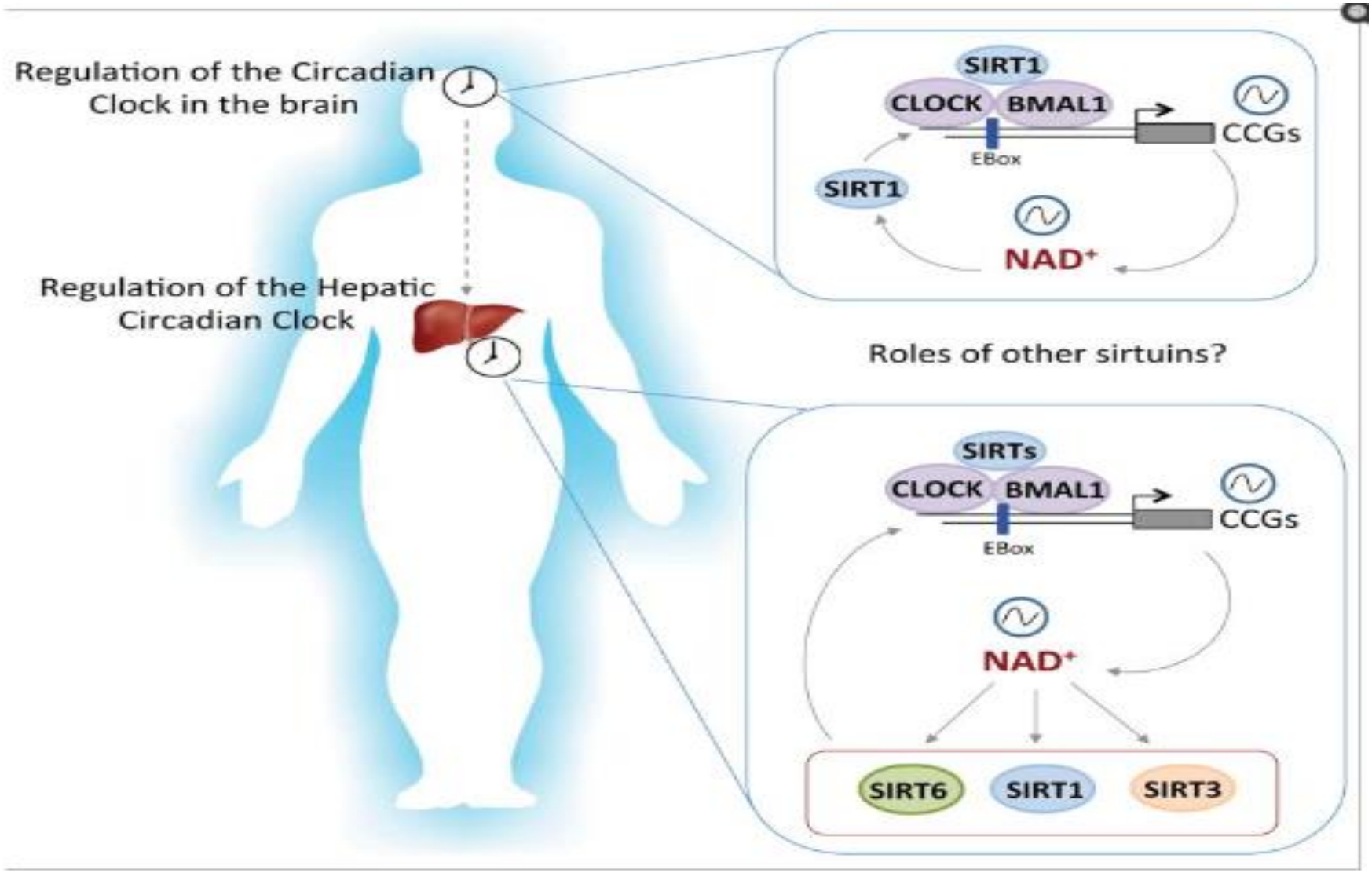
Scheer et al., *PNAS* 2009;106(11)):4453-8

https://en.wikipedia.org/wiki/Suprachiasmatic nucleus

Estrogen – Reproduction - Metabolism



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



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

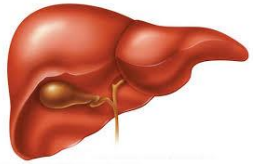
Masri et al. Curr Opin Clin Nutr Metab Care 2015.;18:521-527

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

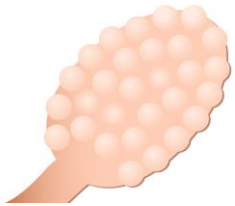
Brain clocks

Vascular clocks

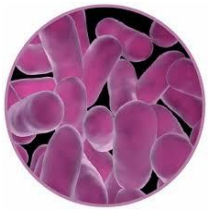


Liver clocks

Bone clocks



Ovarian

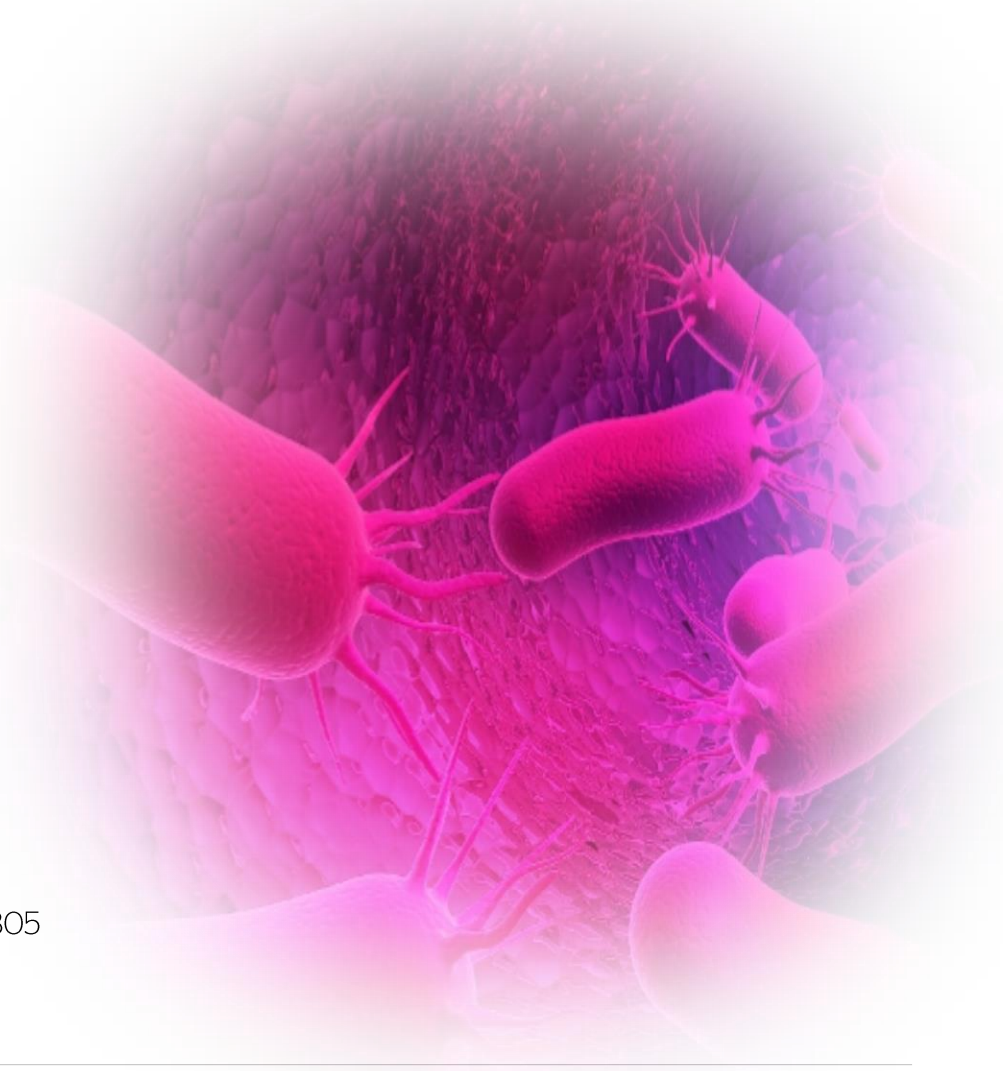


Gut clocks

Gut Microbiome Clock

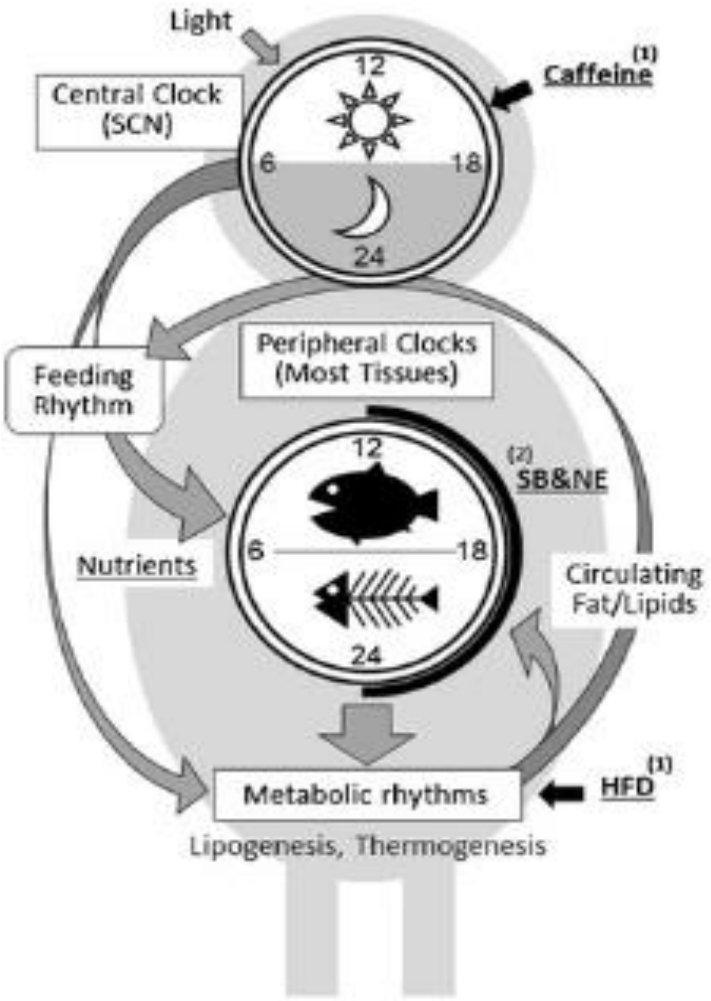
Programmed to anticipate food in the daytime only

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

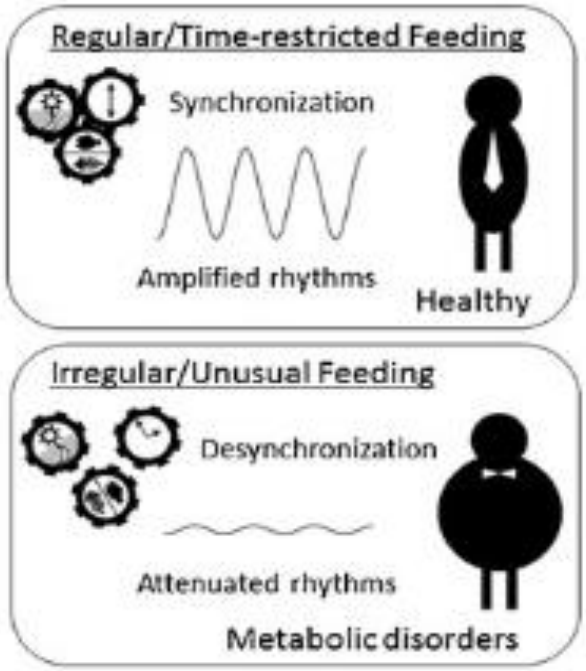
Circadian Rhythm + Intestinal Epithelium



Chrono-nutrition

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

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



Current Nutrition Reports, Curr Nutr Rep. 2014; 3(3): 204–212

Define the Problem and Propose a Solution: My Integrative Approach

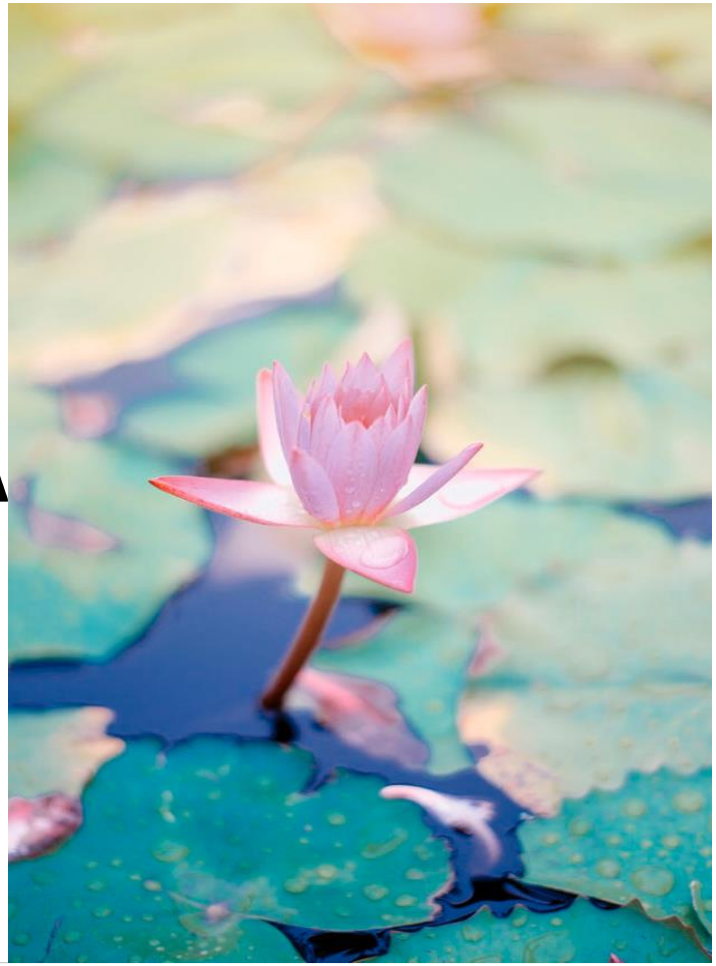
Fitness | **Gynecology** | **Nutrition**

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

My Integrative PCOS SOS
7 Step Program

7 Steps to Optimizing Health for Women with PCOS: Improve Metabolic and Reproductive Health

1. STEP INTO THE LIGHT
2. GET SOME SLEEP
3. EAT TO THE BEAT
4. EXERCISE ANY TIME YOU CA
5. FEED YOUR GUT
6. LIVE CLEAN AND PURE
7. PERSONALIZE YOUR PLAN



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 melatonin (and other supplements)
- 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

Correct the Clock: Sleep Hygiene

3 hours before bed

- Dim the lights
- Minimize computer & electronic use
- Avoid vigorous exercise
- See the sunset if possible

1 hour before bed

- Breathing exercise
- Hot bath
- Calming tea

Sleeping

Cool, dark, quiet room

Upon awakening

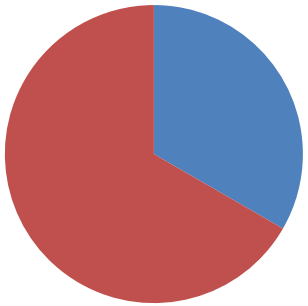
15 minutes of sunlight

Midday sunlight

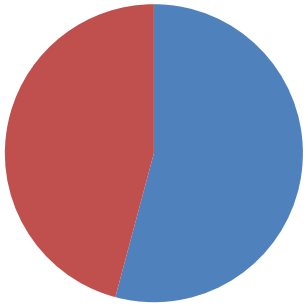
Eat to the Beat

- Eat during the day.
- Fast at night
- Eat big breakfast, moderate lunch, small dinner
- Eat dessert with breakfast
- Eat meals, not snacks
- Chew xylitol gum
- Try longer fasts

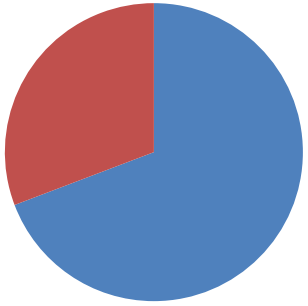
Typical American Meal Pattern



Circadian-Aligned Meal Pattern (A)

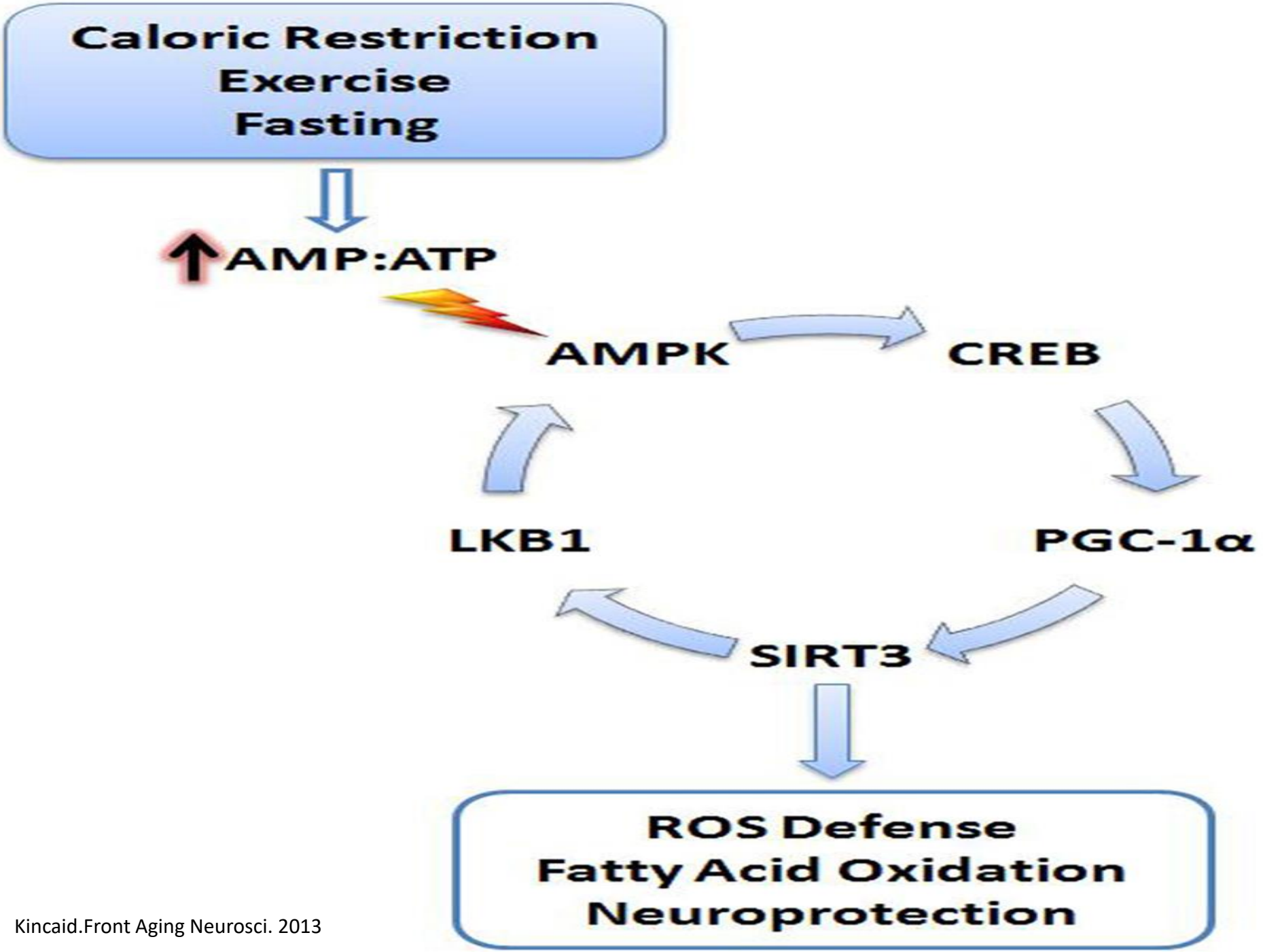


Circadian-Aligned Meal Pattern (B)

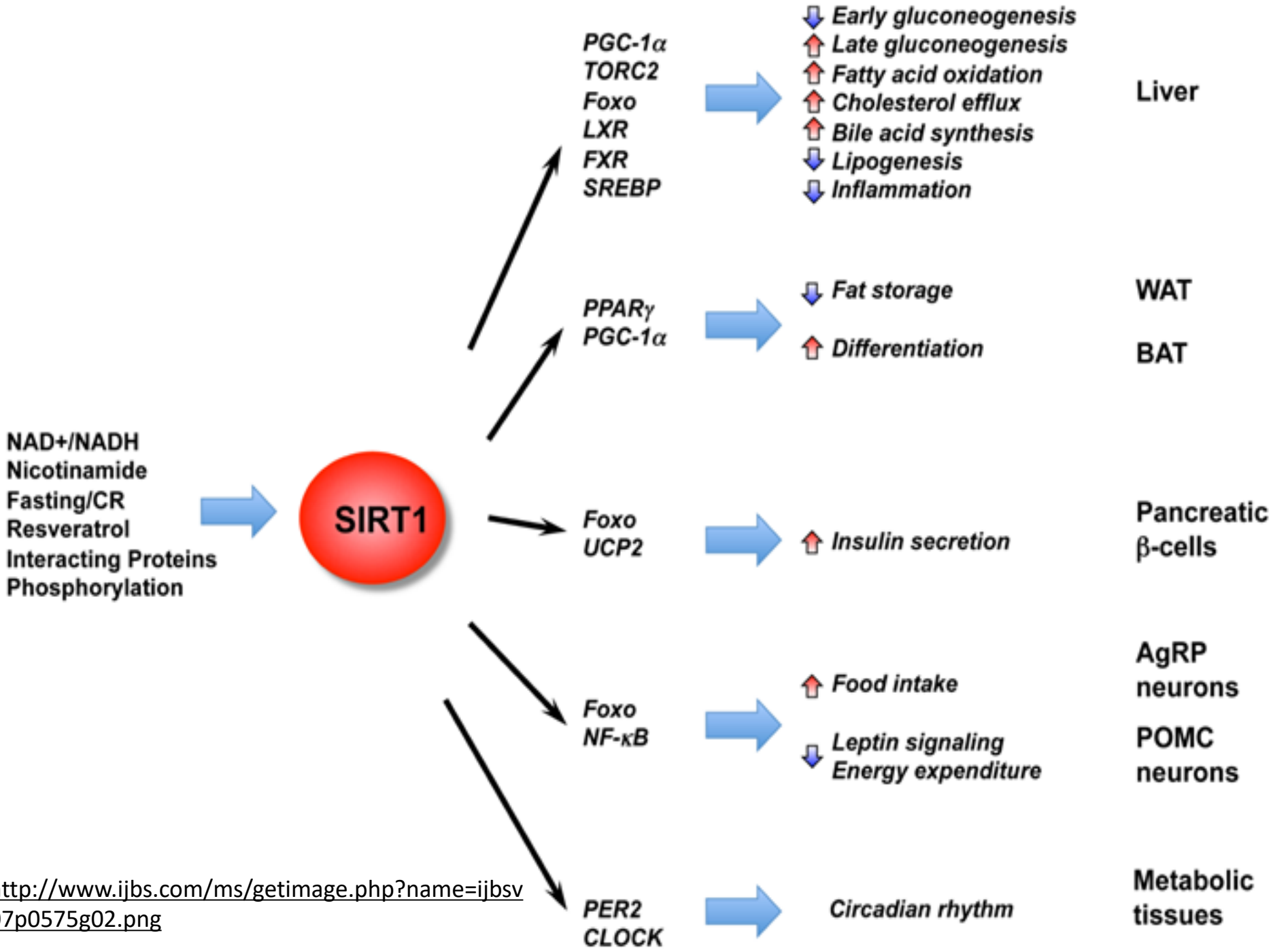


Correct the Clock: Meal Timing

- Eat dinner early
- Eat approximately 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**



Kincaid.Front Aging Neurosci. 2013



http://www.ijbs.com/ms/getimage.php?name=ijbsv07p0575g02.png

Correct the Clock: Meal Timing Matters

Israeli Study:

High caloric intake at breakfast and reduced intake at dinner

Significant changes in:

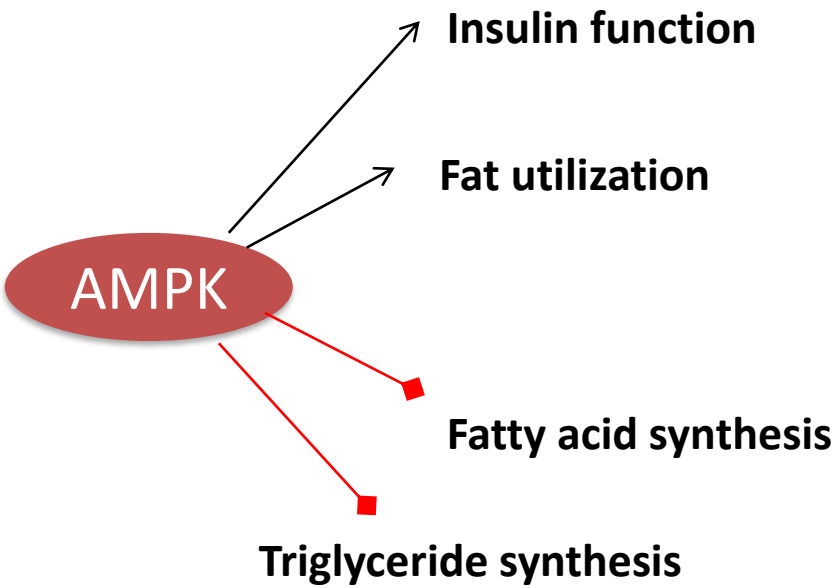
- Glucose – decreased 7 %
- Insulin – decreased 54%
- Testosterone – decreased 50%
- SHBG – increased 105%
- 17 OH progesterone – decreased 39%
- Increased ovulation rate

Jakubowicz et al. Clin Sci. 2013;125(9):423-32 LOE A

Next Best Thing: Fasting Mimetics

Agents that partially emulate metabolic benefits of fasting - support AMPK pathway

Resveratrol
Alpha lipoic acid
Berberine
Exercise



Exercise Every Chance You Get

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

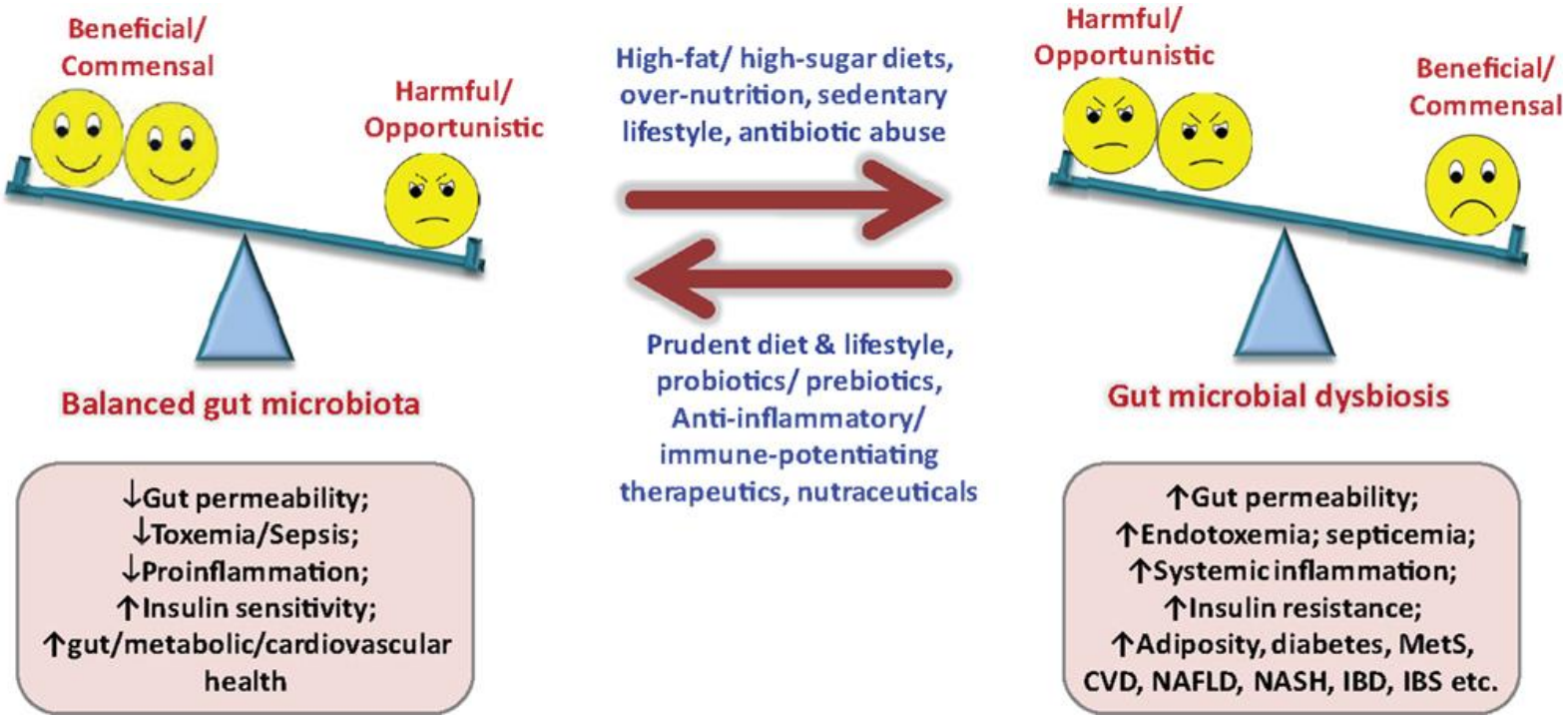
Feed the Gut

- 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
- Take a daily probiotic
- Reboot – eat vegan for 6 months
- Get some great cookbooks, aligned with the plan

Teas

- Chamomile
- Green
- Hibiscus
- Spearmint
- Tulsi
- Lemon grass
- Ginger

Work to Achieve a Healthy Gut Microbiome



"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."

Front. Med., 23 June 2014


Complex carbohydrates
(70% of diet)

Best Diet to Nourish Your Microbiome

INCLUDE	**Complex carbohydrates (70%) whole-grains, all varieties of vegetables, beans, legumes, etc.** **Healthy fats (omega's 3, 6 and 9) from nuts, seeds, olives** **Natural fiber and prebiotic rich foods** **Probiotic rich foods** **Green leafy vegetables and root vegetables**
LIMIT	• **Protein (approximately 12%)**
AVOID	• **Initially, no protein from animals, dairy, or eggs** • **Sugar and refined carbohydrates** • **Alcohol** • **Food intolerances**

Fallucca et al. 2014

Diversity of Microbiome Requires Dietary Diversity

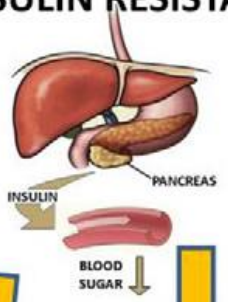
Heiman M et al. *Molecular Metab* 2016;1-4

High fat/ sugar, low fibre diet causes an imbalance between "good" and bad" gut bacteria

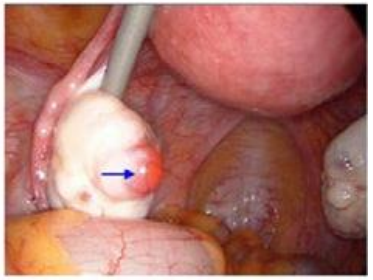
Obesity alters gut micobiota

Obesity directly Increases gut permeability

INSULIN RESISTANCE



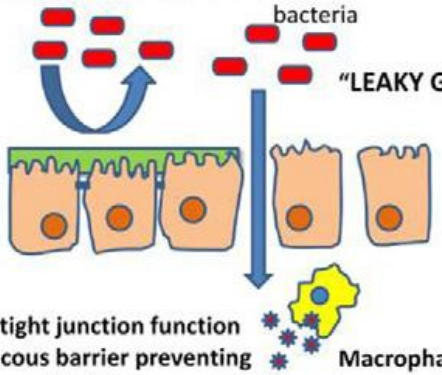
Insulin drives Testosterone Production in ovary, while Impairing follicle development



Gut inflammation initiated
State of Insulin resistance

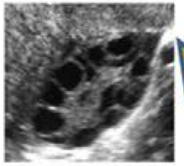
Dysbiosis of colonic microbiota mucous production and epithelial integity- resulting in a "leaky gut"

NORMAL GUT FUNCTION



Normal tight junction function and mucous barrier preventing the trans-epithelial passage LPS

Macrophages activated by bacterial LPS that passes through gut wall

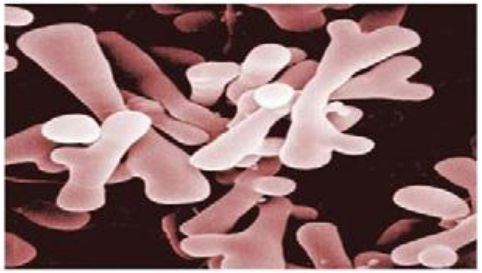


Polycystic morphology On ultrasound

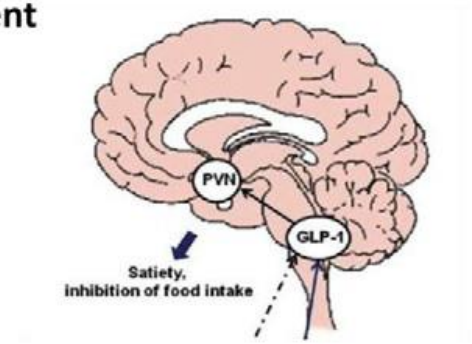
Acne/ hirsuitism

Impaired ovulation

Tremellen et al. Med Hypotheses. 201279(1):104-12



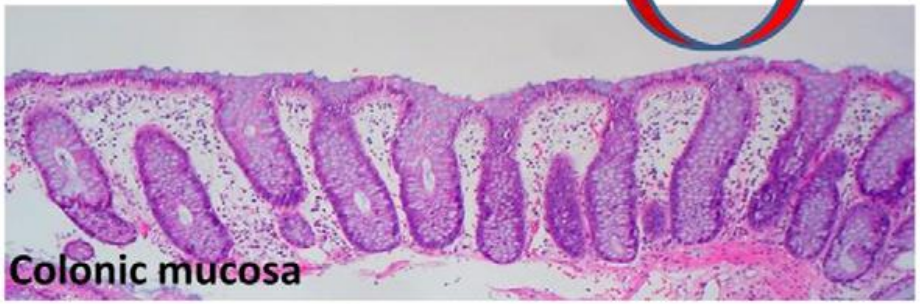
Probiotics and/or prebiotic treatment increases the number of beneficial "good" bacteria in the colon

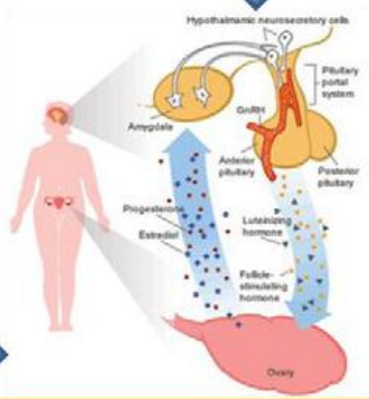


Beneficial "good" bacteria produce Short Chain Fatty Acids (SCFA) that increase colonic mucous production and tight junction function- decreasing the passage of immuno-stimulatory LPS from the colonic lumen into the circulation

Bacterial LPS

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





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

RETURN TO NORMAL OVARIAN FUNCTION

Tremellen et al. Med Hypotheses. 201279(1):104-12

4-week Anti-inflammatory Rest Diet Designed to Support Detoxification and Hormone Metabolism

Product	Morning	Afternoon or Evening
DIM, Ca D Glucurate	1 capsule	1 capsule
NAC 900		1 capsule
Probiotics	1 capsule	
Prebiotic L Glutamine	3 capsules	
EPA/DHA 1 gm	1 capsule	1 capsule

Product	Morning	Afternoon or Evening
Myo-Inositol	1 scoop (2 grams)	1 scoop (2 grams)
Berberine	1 capsule	2 capsules
NAC 900 mg	1 capsule	2 capsules
Vitamin D (1000 – 2000 IU) Capsule or Liquid	1 capsule or 1 drop	
EPA/DHA 1 gram	1 capsule	1 capsule
Chromium **Alpha Lipoic Acid** **Cinnamon** **Quercetin** **Curcumin/Turmeric** **Resveratrol** ---------- **Melatonin** ---------- **Nitric Oxide Booster**		3 – 6 mg, .5 mg a few hrs earlier

N-Acetyl Cysteine

- Precursor component to glutathione - master anti-oxidant and detoxifier
- Improves hyperglycemia
- Free radical scavenger
- Inhibits hyperglycemic-induced ROS production and hyperglycemia-induced DNA damage
- Benefits liver and kidneys
- Reduces pro-inflammatory response in adipose tissue
- Dose: 500-1800 mg tid

Myo-Inositol

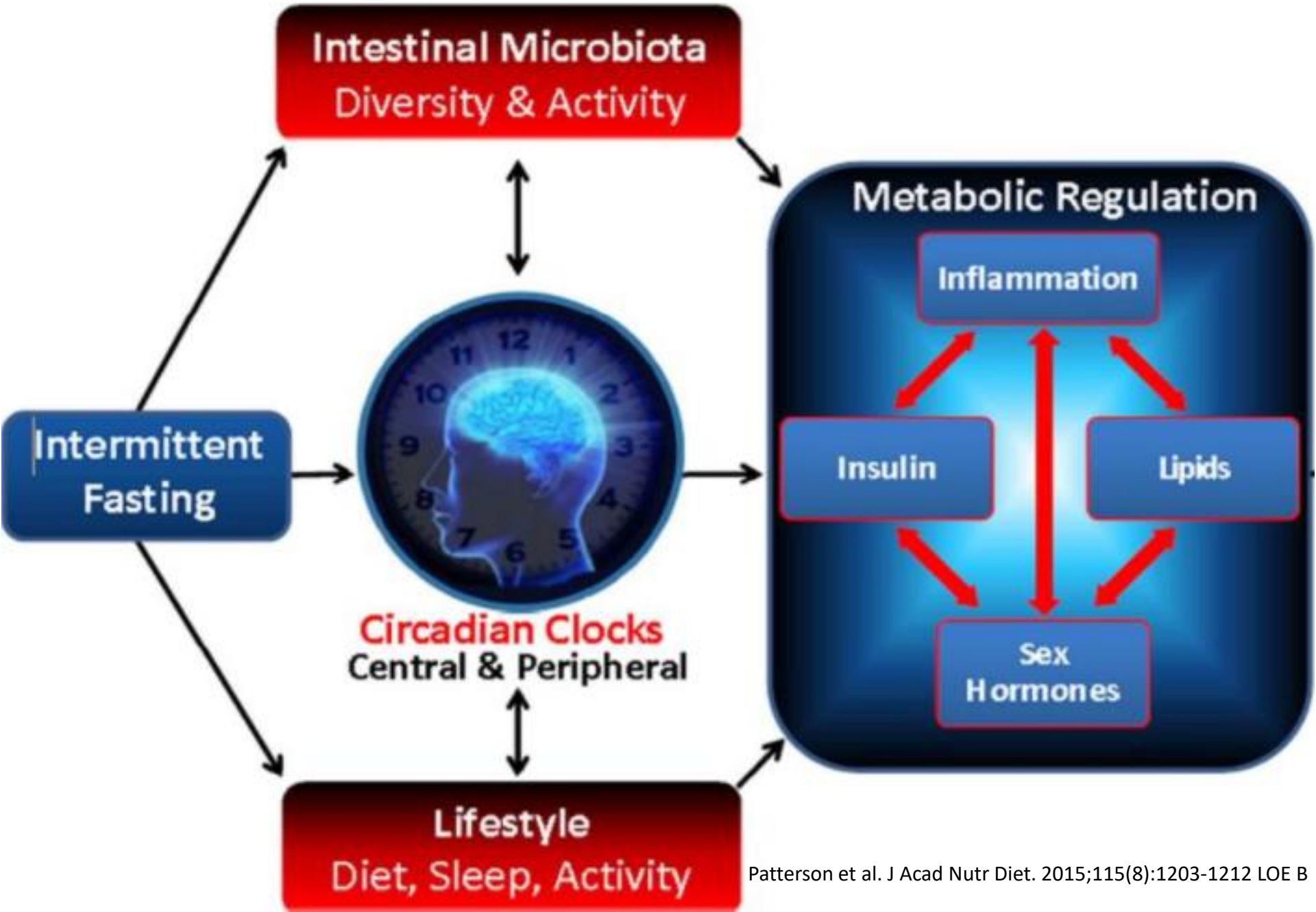
- Myo-inositol and D-chiro-inositol improve insulin resistance and hyperandrogenism
- Induces ovulation in PCOS women. Myo-inositol restored ovulation – consistent data, while data on D-chiro-inositol not consistent
- Comparative study: myo-inositol had a specific benefit on the ovary. DCI supplementation reduced oocyte quality – exercise care in quantity of D-chiro-inositol used

J Ovarian Res. 2012; Published online 2012 May 15 Does ovary need D-chiro-inositol?

Berberine

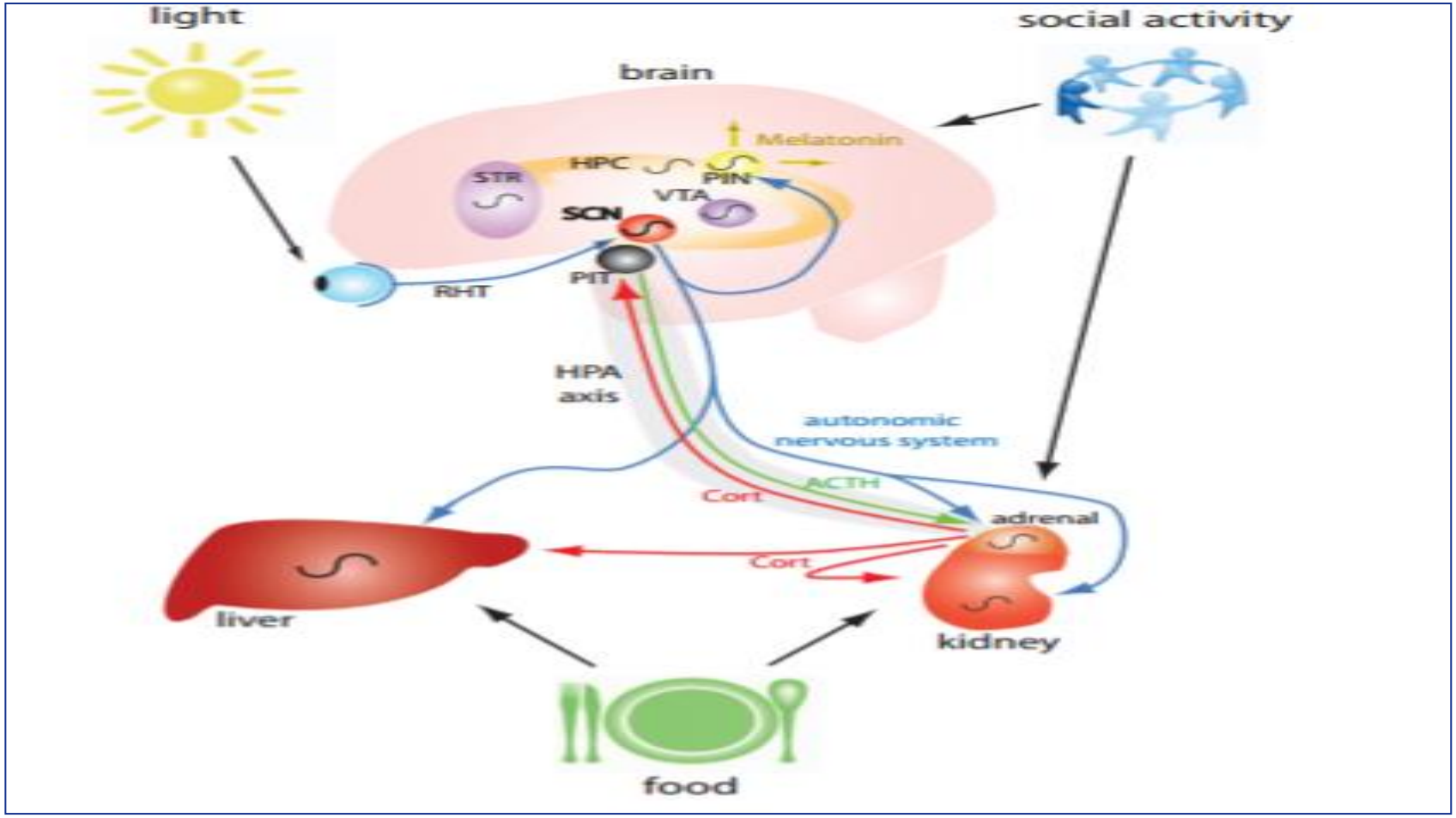
- Isoquinoline alkaloid isolated from several herbs including *Rhizoma Coptidis*
- Chinese medicine - treatment of gastrointestinal infections, diarrhea, cardiovascular diseases, inflammation and hypercholesterolemia
- Improves clinical, metabolic, and reproductive features in PCOS women.
- Improved defective uptake of glucose by theca cells and reduced excessive production of testosterone by theca cells
- Treatment of type 2 diabetes - studies using human patients, animals, and insulin sensitive cell lines establish clear hypoglycemic effect of berberine.

Berberine Reduces Insulin Resistance; Fertility and Sterility, Vol 95, Feb 2011 LOE B



Patterson et al. J Acad Nutr Diet. 2015;115(8):1203-1212 LOE B

Path to Hormonal Health – Metabolic Health – Fertility Optimization



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

Thank You!

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