EXCLUSIVE LIVE WEBINAR

Unlocking the Body's Clock:
The Powerful Connection Between Food, Behavior, and Circadian Rhythms

EARN
1.5 CEUs

PRESENTED BY

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M.Ed., RD, LDN, CDCES

January 10, 2024
2-3:30pm ET

Disclosures

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This activity will also award credit for dietetics (CDR CPEU).

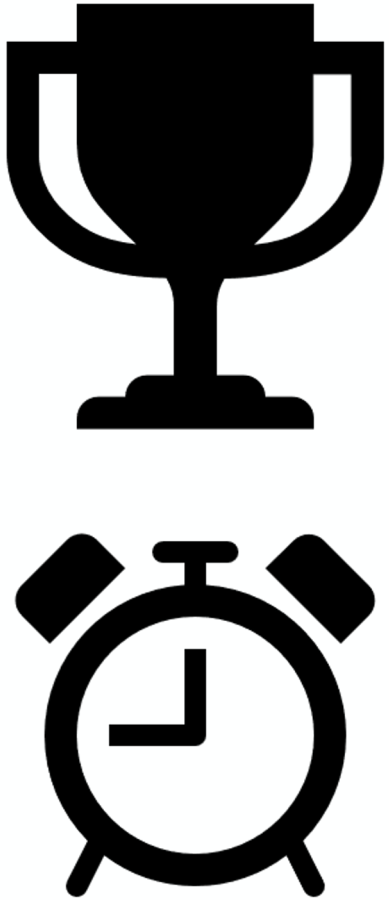
Learning Objectives

Describe	Define	Analyze	Describe	State
Describe the coordinated role played by the central and peripheral biological s in regulating the body's circadian rhythms.	Define chrono-nutrition and explain why synchronization of the endogenous circadian system with food, behavior (exercise/sleep), and endocrine factors is crucial to health.	Analyze the bi-directional interactions between the gut microbiome and host circadian rhythms in influencing metabolism.	Describe the mechanism by which circadian rhythm misalignment leads to an array of metabolic disruptions.	State how and why RDs need to stay on the leading edge of the emerging research on chrono-nutrition to help their patients eat and live healthfully.

The Clock Rules. Time Matters.

What are circadian rhythms?

- Precisely timed endogenous rhythms that adapt our physiology to a rapidly changing external environment
- Critical functions such as behavior, hormone levels, sleep, body temperature, and metabolism
- Nobel prize for medicine in 2017
- Gene controlling circadian rhythms isolated
- Proteins that dictate *what functions to carry out at what time of day* identified
- A mismatch between the internal time-keeper and the external environment can lead to metabolic disease



Huang RC. *Biomed J*. 2018

Endogenous Clocks Are Autonomous

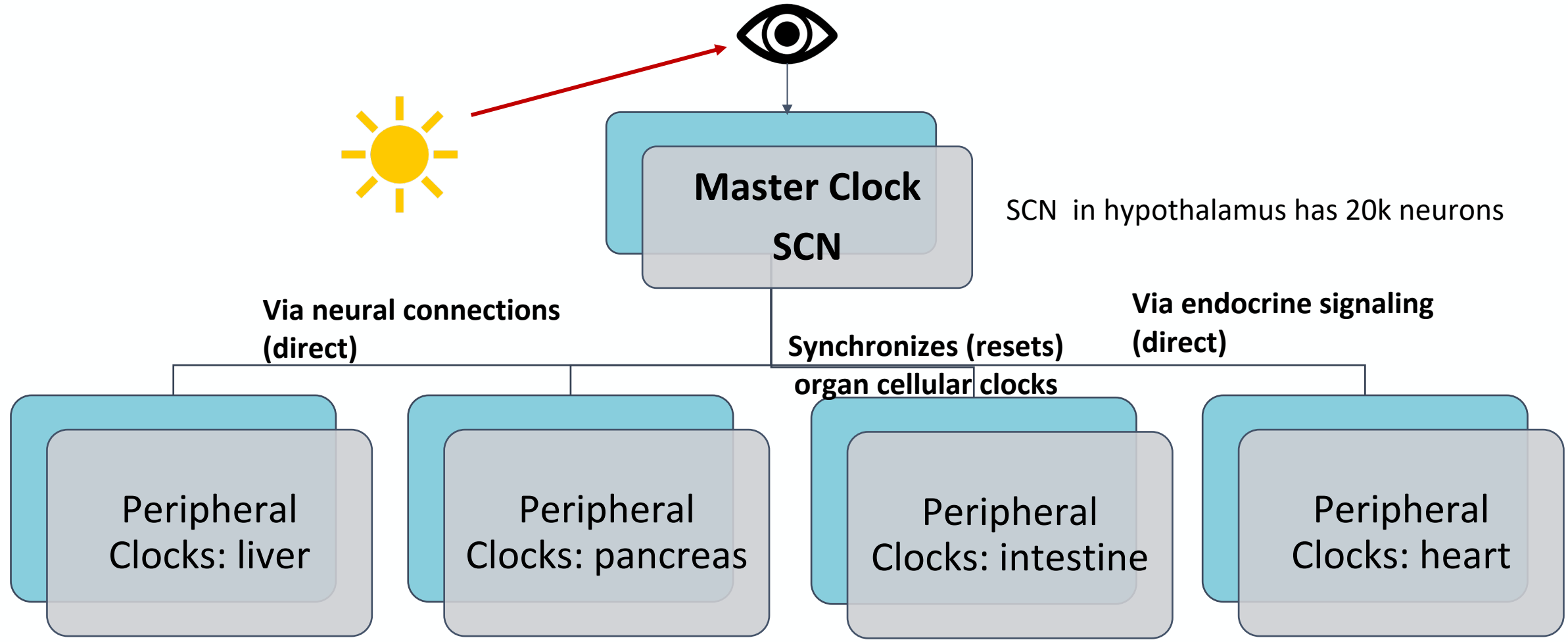
- Night follows day in a predictable rhythm
- Evolution of intrinsic, circadian clocks
  - Regulate our physiology and behavior, synchronizing them to the appropriate time of day
- *Anticipatory* mechanisms that adapt to daily fluctuations
- Autonomous/self-sustaining
- Entrainment to an external input, most notably the light-dark cycle to prevent “drifting”

Huang RC. *Biomed J*. 2018

The Synchronization of the Central and Peripheral Clocks

Creates robust circadian rhythms, enhances metabolic health

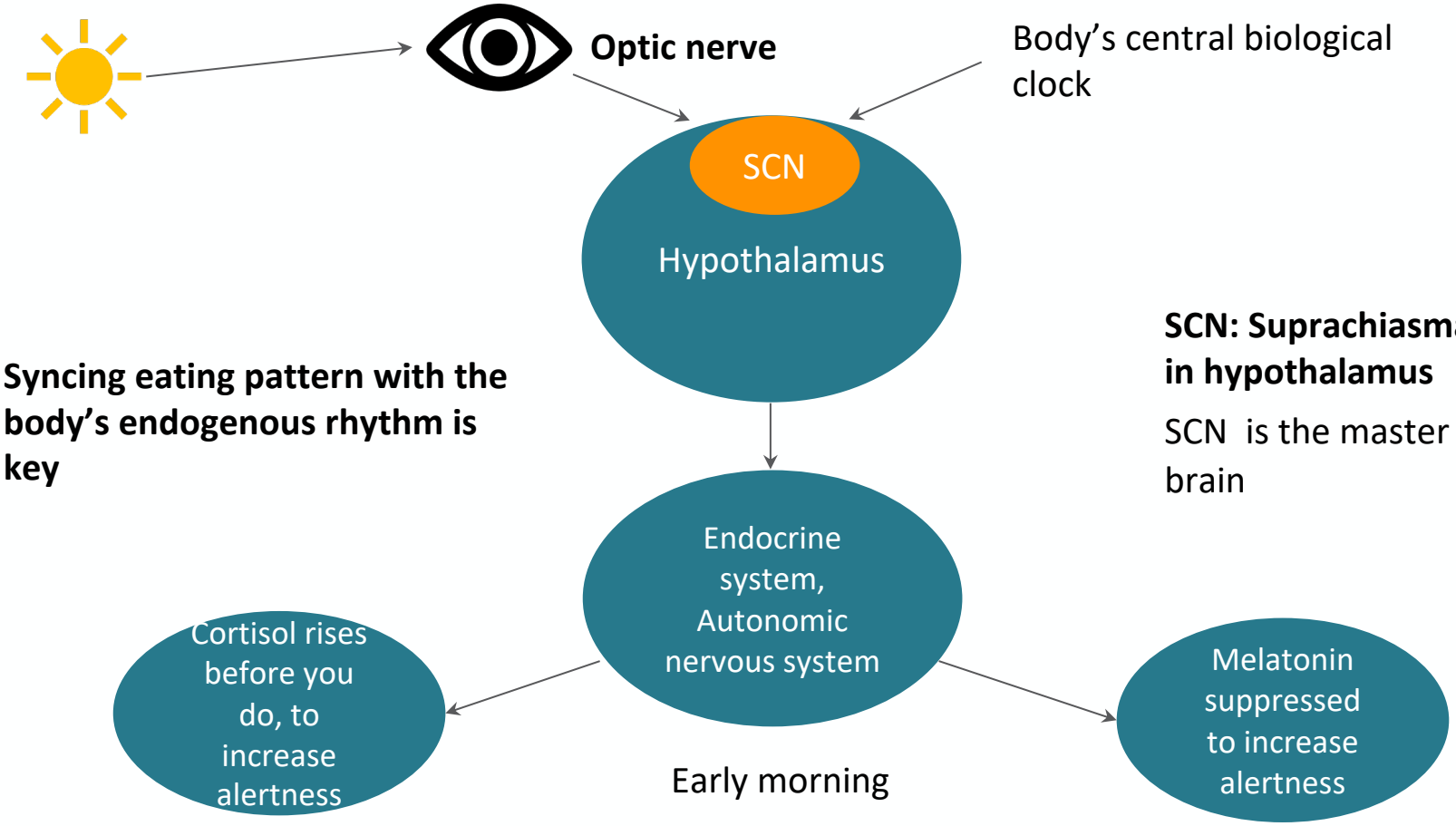
Once SCN* is Activated with Light, it Signals the Time for Key Functions to the Organ Clocks



*SCN = suprachiasmatic nucleus

Flanagan A, Bechtold DA, Pot GK et al. *Neurochem*. 2021

SCN Dictates Sleep-Wake Cycle Through Hormonal Release



Syncing eating pattern with the body's endogenous rhythm is key

SCN: Suprachiasmatic nucleus in hypothalamus

SCN is the master clock in the brain

Adapted from: Zarrinpar A, Chaix A, Panda S et al. *Trends Endocrinol Metab. 2016*

The SCN Controls the Release of Cortisol, a Key Hormone

Hypothalamus

- CRH or Corticotrophin releasing hormone

Anterior Pituitary

- ACTH or Adrenocorticotropic hormone

Adrenal cortex

- Cortisol, robust time of day dependent rhythm

Nicolaides NC, Charmandari E, Chrousos GP et al. *Ann N Y Acad Sci* **2014**

What are Zeitgebers?

What is Their Significance?

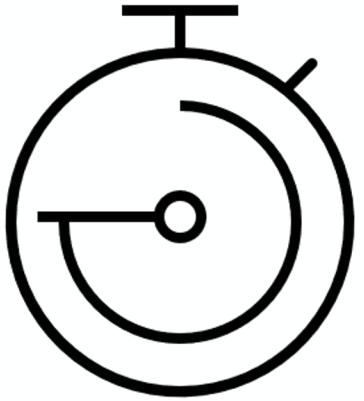
- Literally means “time giver”
- Refers to any **resetting** stimulus from the environment
- **Light** is a universal and potent zeitgeber to the SCN
- **Food timing and schedule** is a potent zeitgeber for non-SCN clocks
- Light indirectly affects peripheral clocks through signals from the SCN
- Feeding behavior resets peripheral clocks without shifting the SCN phase
- This leads to a misalignment between central and peripheral rhythms
- Entraining the master clock daily to the external light-dark cycle to prevent drifting out of phase

Flanagan A, Bechtold DA, Pot GK et al. *J Neurochem*. 2021
Pickel L, Sung HK. *Front Nutr*. 2020

Why Do We Need Circadian Clocks?

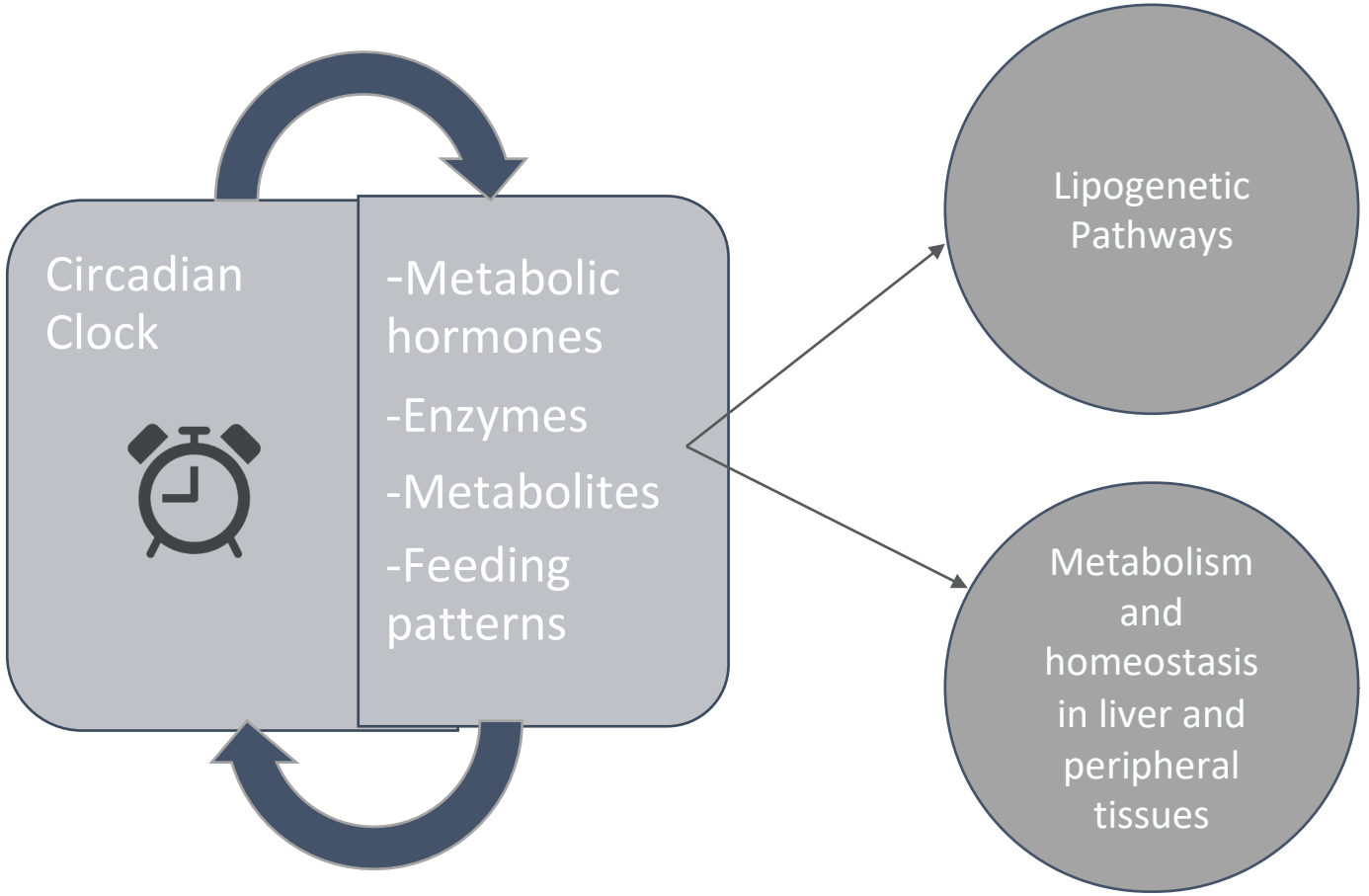
Timing is Everything

1. The right hormone at the right time!
2. Cortisol and melatonin cannot be secreted simultaneously, as they have opposing functions.
3. Prevents potentially incompatible processes from occurring simultaneously.
4. Endocrine factors oscillate over 24 hours.
5. The SCN is “mission control,” driving the circadian expression of genes, hormones, and enzymes involved in metabolism.
6. Creates an exquisitely-timed circadian rhythm …unless this is disrupted.



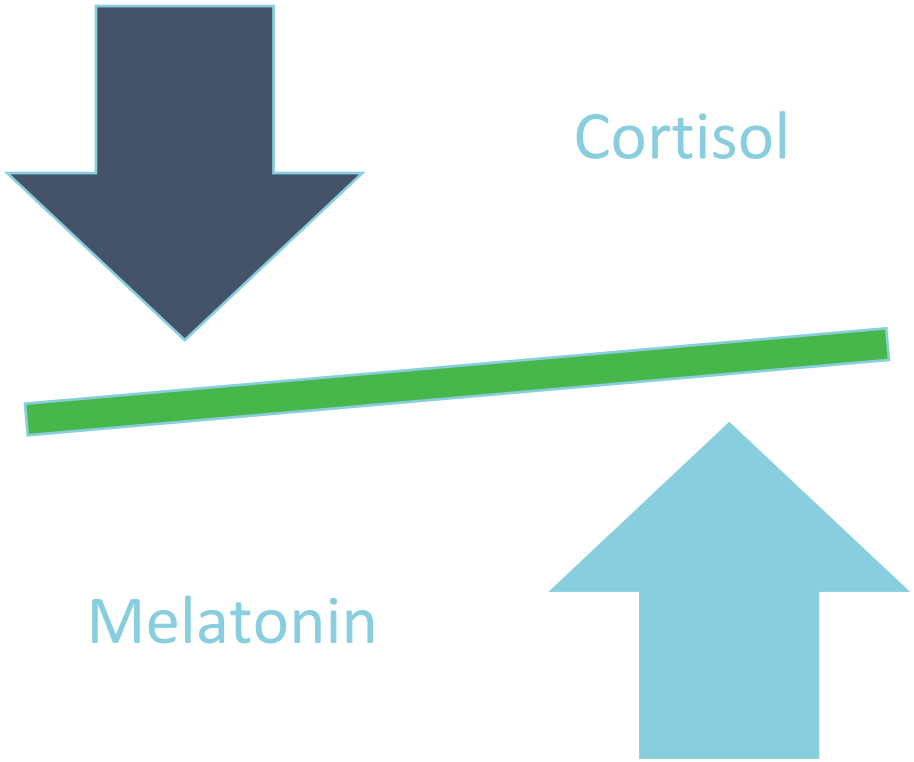
Pickel L, Sung HK. *Front Nutr*. 2020

Reciprocal Feedback Loop Between Circadian Clock and Hormones/Enzymes



Grosjean E, Simonneaux V, Challet E et al. *Biology (Basel)*. 2023

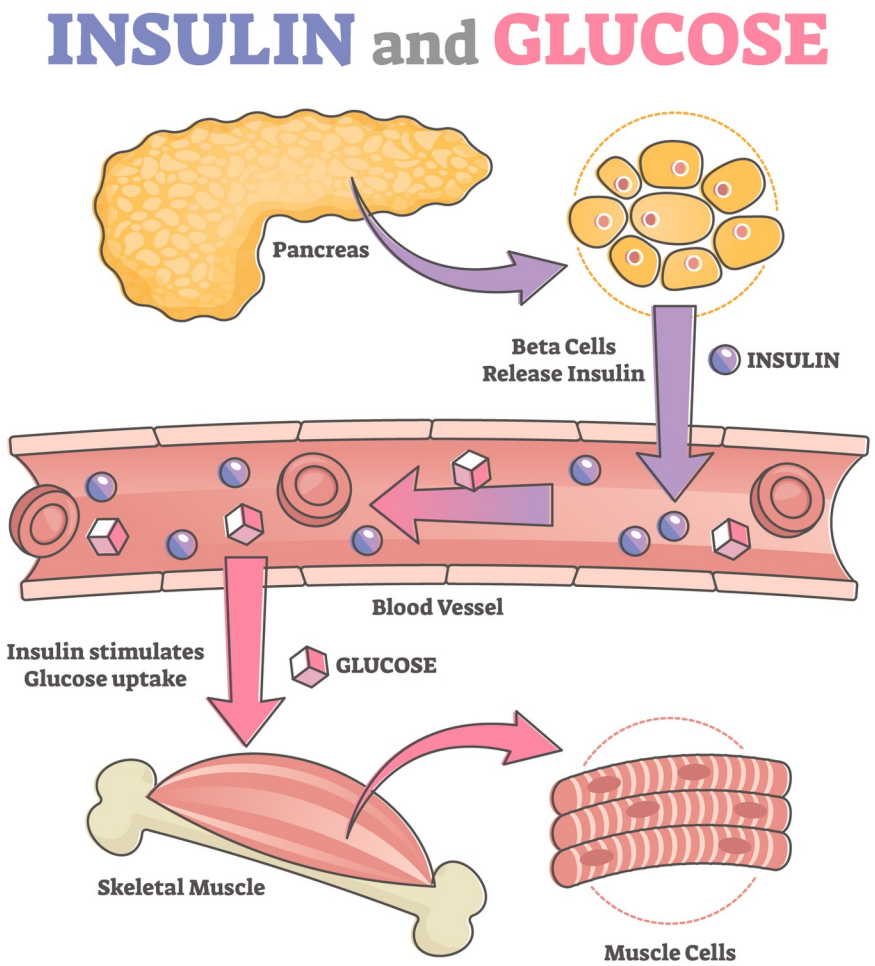
Both Display Diurnal Rhythm, Under SCN Control



Zarrinpar A, Chaix A, Panda S. *Trends Endocrinol Metab*. 2016
Owino S, Buonfiglio DDC, Tchio C et al. F*ront Endocrinol (Lausanne)*. 2019

Hormone	Time-of-day-dependent Rhythm	Time of Peak	Citation
Cortisol	Yes	0700–0800h	Kalsbeek *et al*[16]; Carroll *et al*[3]
Growth Hormone	Yes	Pulsatile secretion, with Increased amplitude at night	Avram *et al*[1]; Jaffe *et al*[20]; Villadolid *et al*[21]; Goji *et al*[22]
Follicle-stimulating hormone (females)	No	NA	Klingman *et al*[153]
Testosterone (males)	Yes	0700h	Walton *et al*[5]
Prolactin	Yes	0200h (amplitude larger in females)	Freeman *et al*[4]
Thyroid stimulating hormone	Yes	0100–0200h	Russell *et al*[2]
Triiodothyronine	Yes	0230–0330h	Russell *et al*[2]
Thyroxine	No	NA	Russell *et al*[2]
Renin-angiotensin-aldosterone system	Yes	Early morning	White *et al*[154]
Fibroblast growth factor 21	Yes	0500–0800h	Lee *et al*[155]; Yu *et al*[156]
Ghrelin	Yes	0200–0430h (fed state) 1300h (fasted state)	Koutkia *et al*[157]; Natalucci *et al*[158]
Adiponectin	Yes	1200–1400h	Scheer *et al*[7]; Gavrila *et al*[23]
Leptin	Yes	0100h	Gavrila *et al*[23]
Vasopressin	Yes	Middle of night	Forsling *et al*[159]
Insulin	Yes	1700h	Goel *et al*[6]
Melatonin	Yes	Middle of night	Van Cauter *et al*[36]

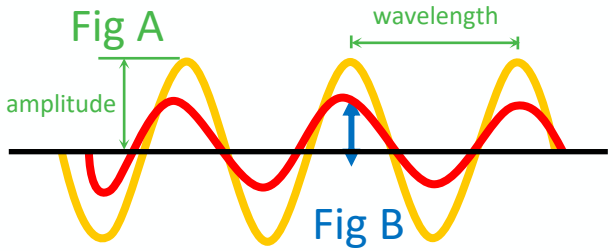
Insulin



- Nutrient sensing hormone
- Anabolic, inhibits beta oxidation of fatty acids, promotes fat storage
- Insulin secretion displays a diurnal rhythm in humans, peaking at roughly 1700h
- Insulin sensitivity highest in the am

Saad A, Dalla Man C, Nandy DK, et al. *Diabetes*. 2012

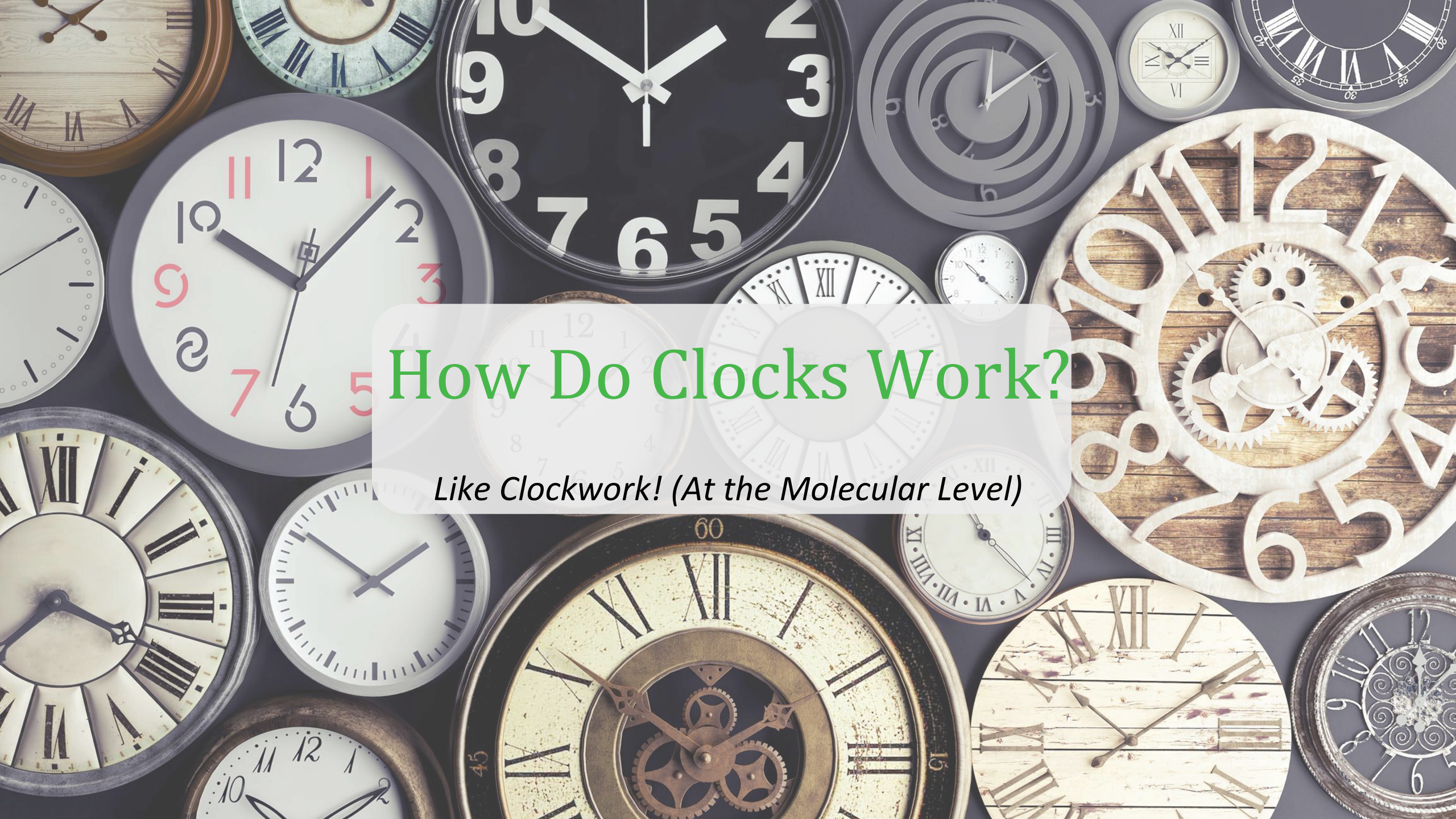
Leptin Weakening of Rhythms (Amplitude) in Obesity



Leptin weakening of rhythms (amplitude) in obesity

- Leptin, acts to suppress appetite, increase metabolism
- Plasma leptin peaks early in the nonactive phase in diurnal beings
- Under SCN control
- In **obese** subjects, leptin rhythms have a lower amplitude
- The weaker rhythm contributes to leptin resistance and obesity
- Also, loss of feeding rhythms ***precedes obesity*** in leptin-deficient mice (mutants)
- Desynchronized feeding adversely affect the endogenous rhythm of leptin, leading to weight gain

Turek FW, Joshu C, Kohsaka A, et al. *Science*,2015
Graph adapted from: Ducksters, Physics for kids: Properties of waves



How Do Clocks Work?

Like Clockwork! (At the Molecular Level)

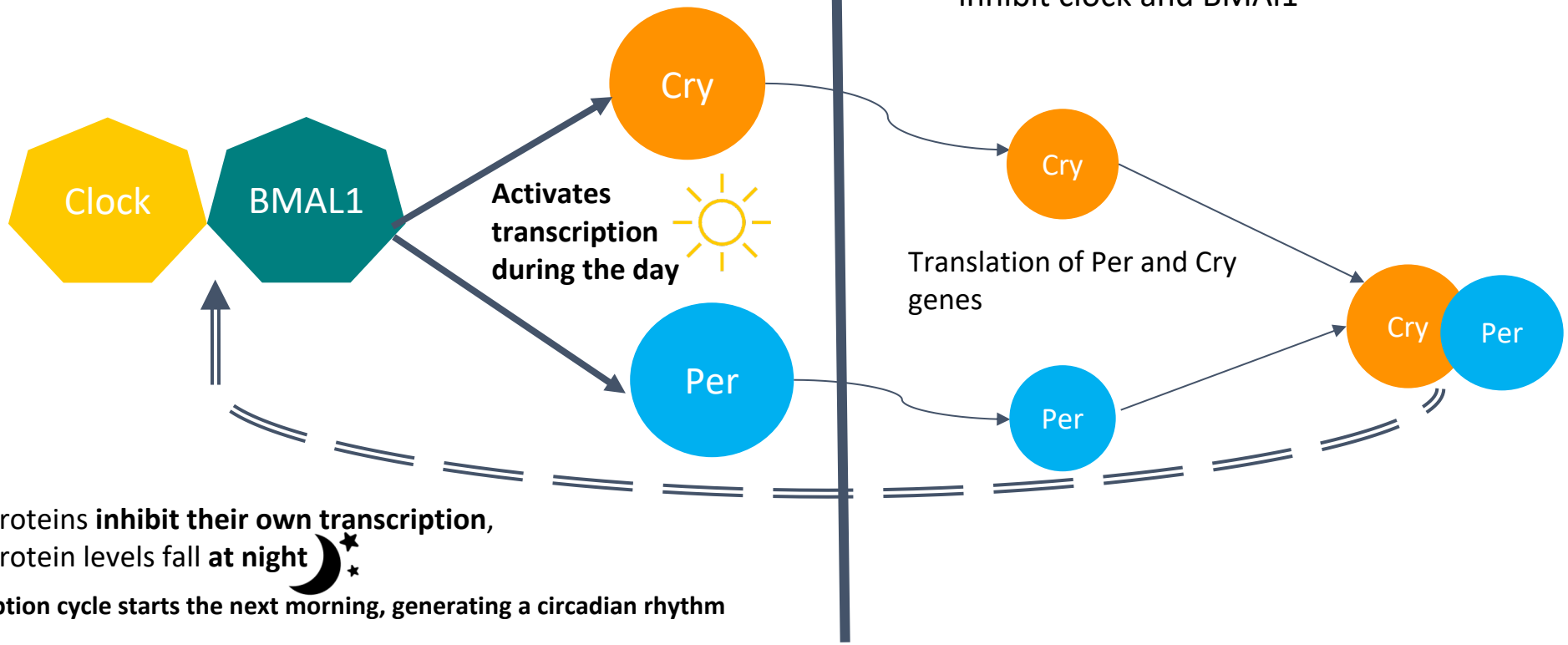
Transcription-Translation Feedback Loop is Key to the Core-Clock Mechanisms

Nucleus

- Clock (transcription factor) dimerizes with BMAL1, another transcription factor

Cytoplasm

- After transcripts of Per and Cry are translated in the cytoplasm, they dimerize and return to the nucleus to inhibit clock and BMAl1



Per and Cry proteins **inhibit their own transcription**,
Per and Cry protein levels fall **at night**

A new transcription cycle starts the next morning, generating a circadian rhythm

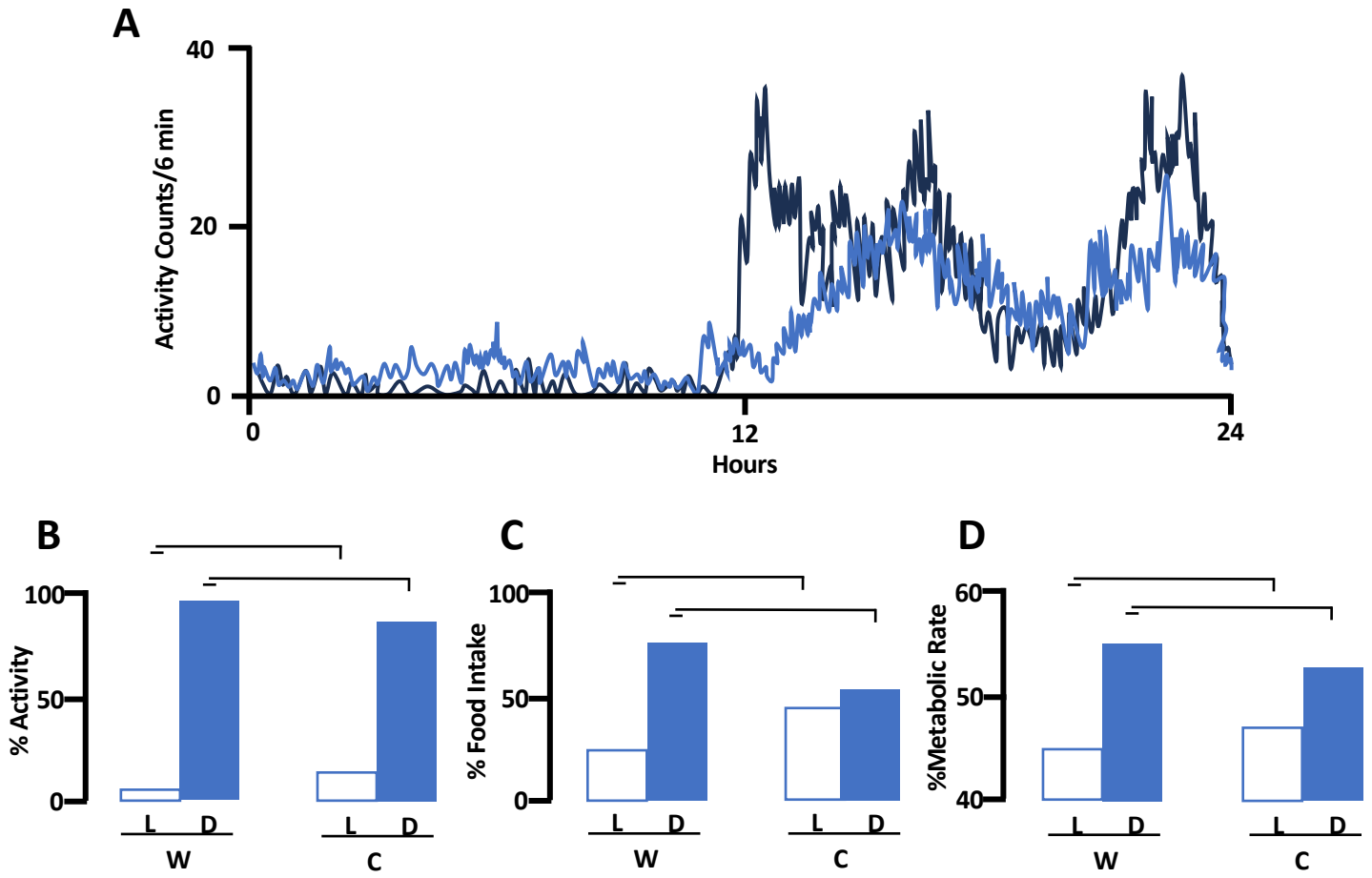
Richards J, Gumz ML. *Physiol Regul Integr Comp Physiol*. 2013
Huang RC. *Biomed J*. 2018

Molecular Basis of the Clock
Are you a morning lark or a night owl?

- The rate at which clock proteins are degraded during a transcription-translation feedback loop determines the length of the circadian cycle
- Quicker degradation at night: shorter cycle: morning lark (advanced phase)
- Slower degradation at night: longer cycle: night owl (delayed phase)

Richards J, Gumz ML *Am J Physiol Regul Integr Comp Physiol*. 2013

Altered Diurnal Rhythms in Locomotor Activity, Feeding and Metabolic Rate in *Clock* Mutant Mice

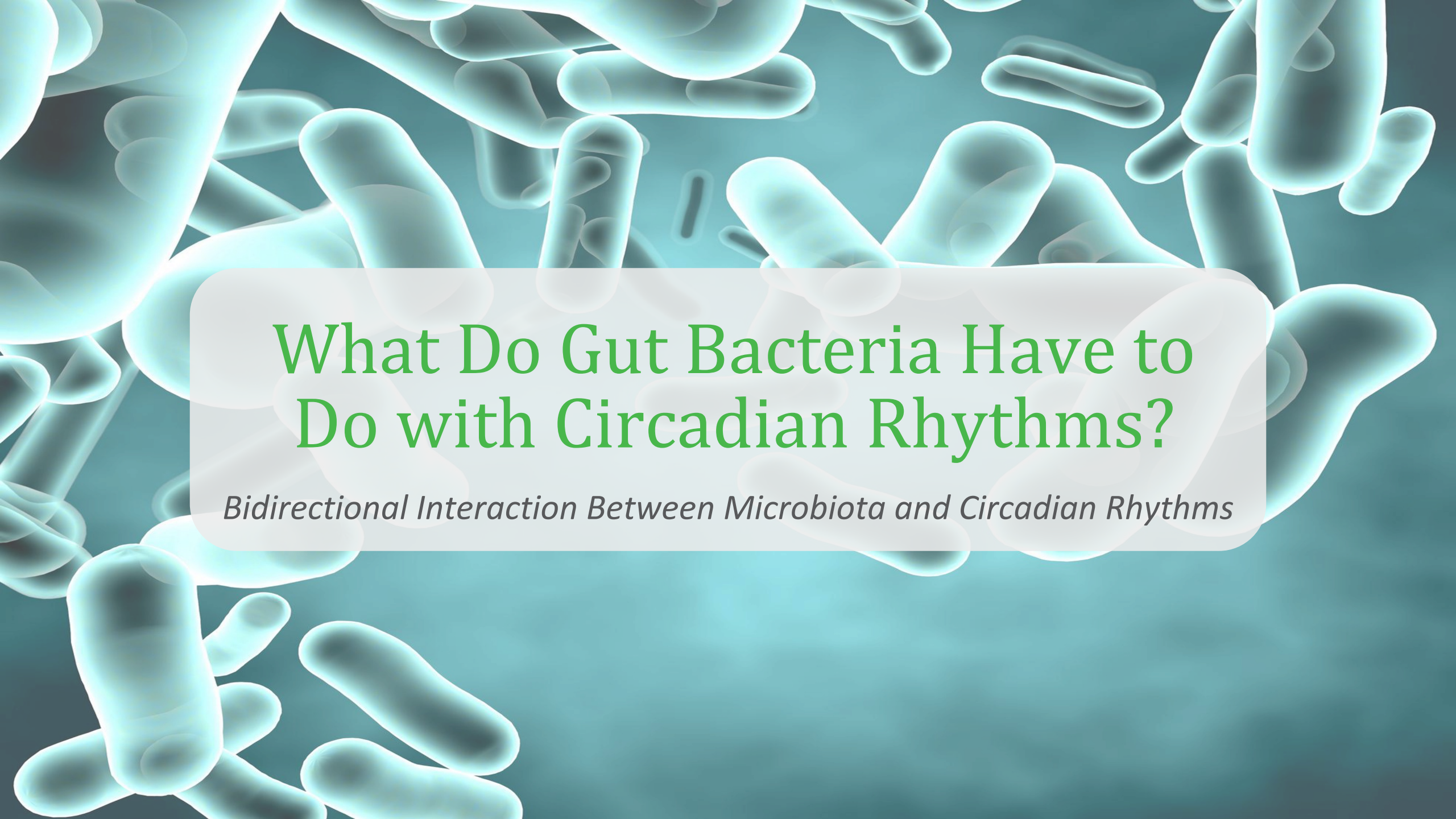


Adapted from: Turek FW, Joshu C, Kohsaka A, et al. Obesity and metabolic syndrome in circadian clock mutant mice. *Science*. 2005;308(5724):1043-1045. doi:10.1126/science.1108750

Effect of Clock Gene Mutation on Key Markers

Metabolic parameters	Wild Type	Clock mutant	P value
Triglyceride (mg/dl)	136 ± 8	164 ± 8	$P < 0.05$
Cholesterol (mg/dl)	141 ± 9	163 ± 6	$P < 0.05$
Glucose (mg/dl)	130 ± 5	161 ± 7	$P < 0.01$
Insulin (ng/ml)	1.7 ± 0.3	1.1 ± 0.1	N.S.
Leptin (ng/ml)	3.4 ± 0.4	4.6 ± 0.3	$P < 0.05$

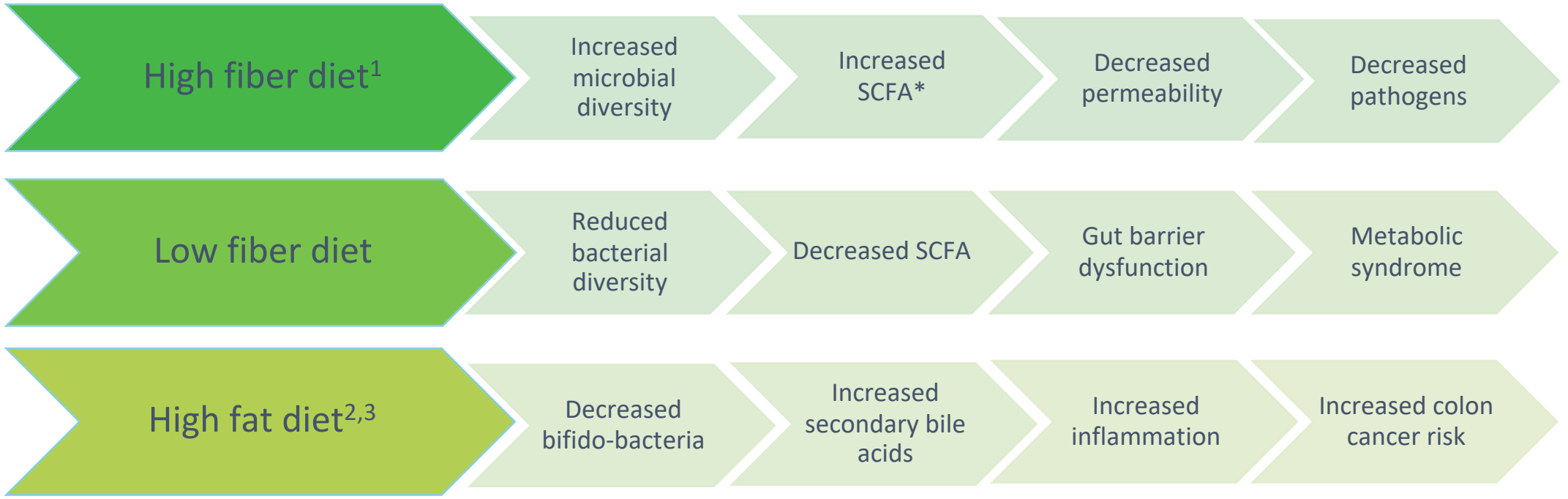
Adapted from: Turek FW, Joshu C, Kohsaka A, et al. Obesity and metabolic syndrome in circadian clock mutant mice. *Science*. 2005;308(5724):1043-1045. doi:10.1126/science.1108750



What Do Gut Bacteria Have to Do with Circadian Rhythms?

Bidirectional Interaction Between Microbiota and Circadian Rhythms

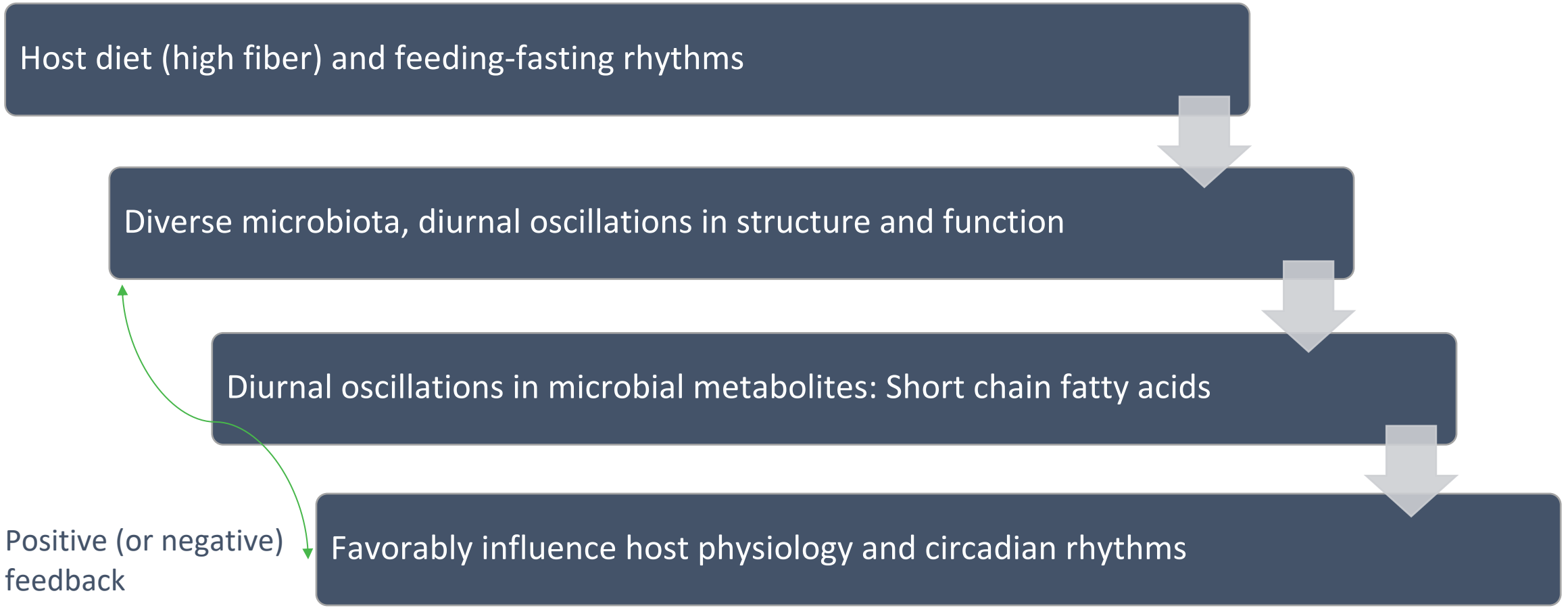
Contrasting Diet Effects



*strengthens intestinal barrier, maintains normal mucosal function

1. Fu J, Zheng Y, Gao Y, Xu W. *Microorganisms*. 2022
2. Murphy EA, Velazquez KT, Herbert KM. *Curr Opin Clin Nutr Metab Care*. 2015
3. Zeng H, Umar S, Rust B et al. M. *Int J Mol Sci*. 2019

Bidirectional Link Between Microbiome and Host Circadian Rhythms

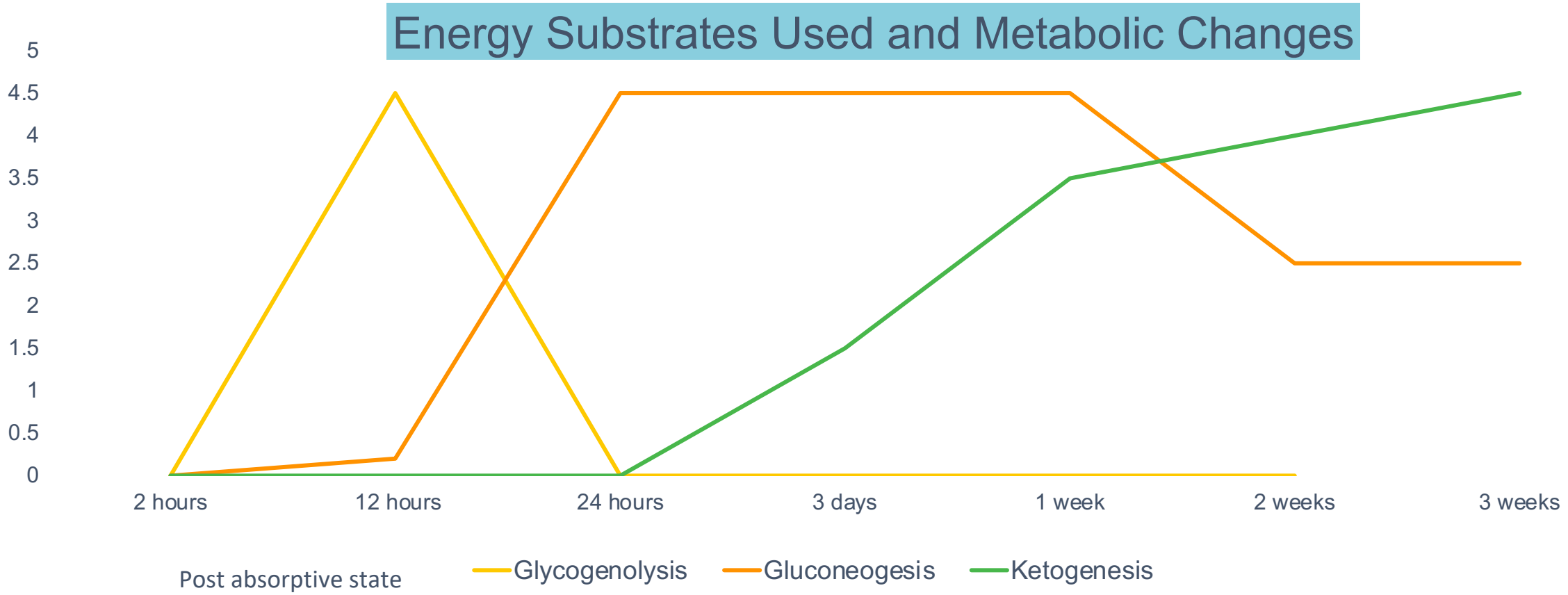


Gutierrez Lopez DE, Lashinger LM, Weinstock GM et al. *Cell Metab*. 2021

Intermittent Fasting and Circadian Rhythms

How Are They Linked?

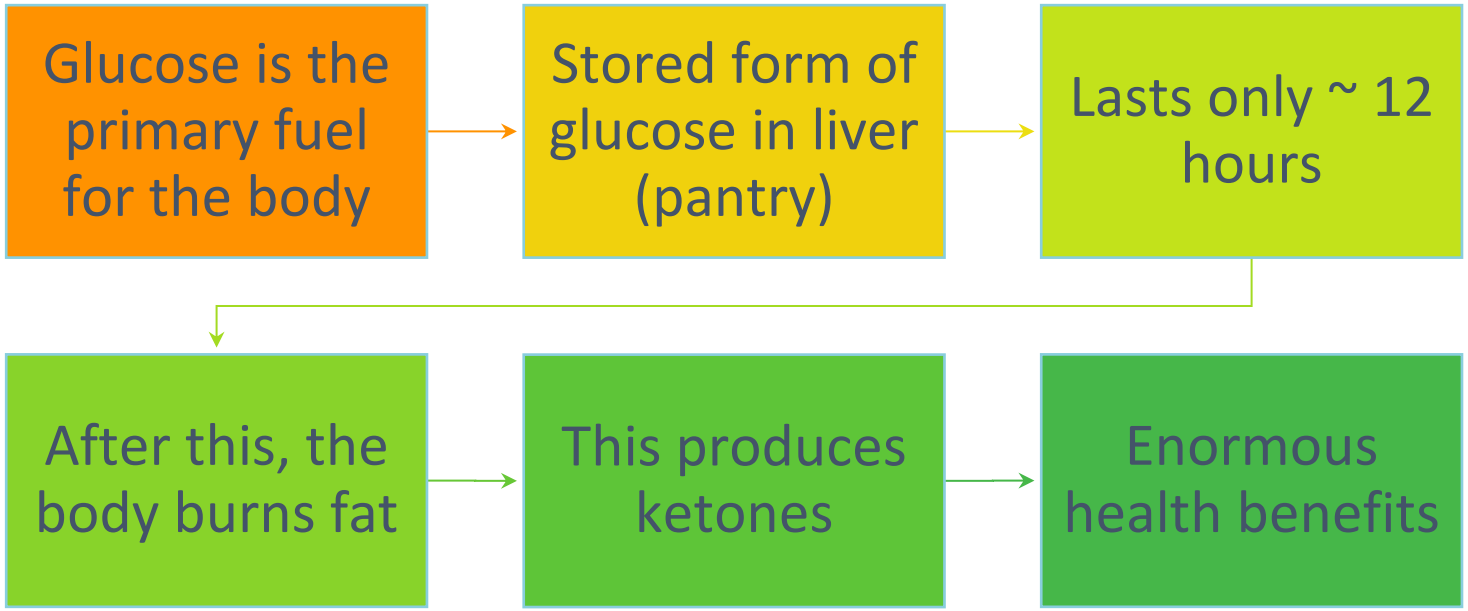
Metabolism of Fasting



Wang Y, Wu R. *Dis Markers*. 2022
Longo VD, Mattson MP. *Cell Metab.* 2014

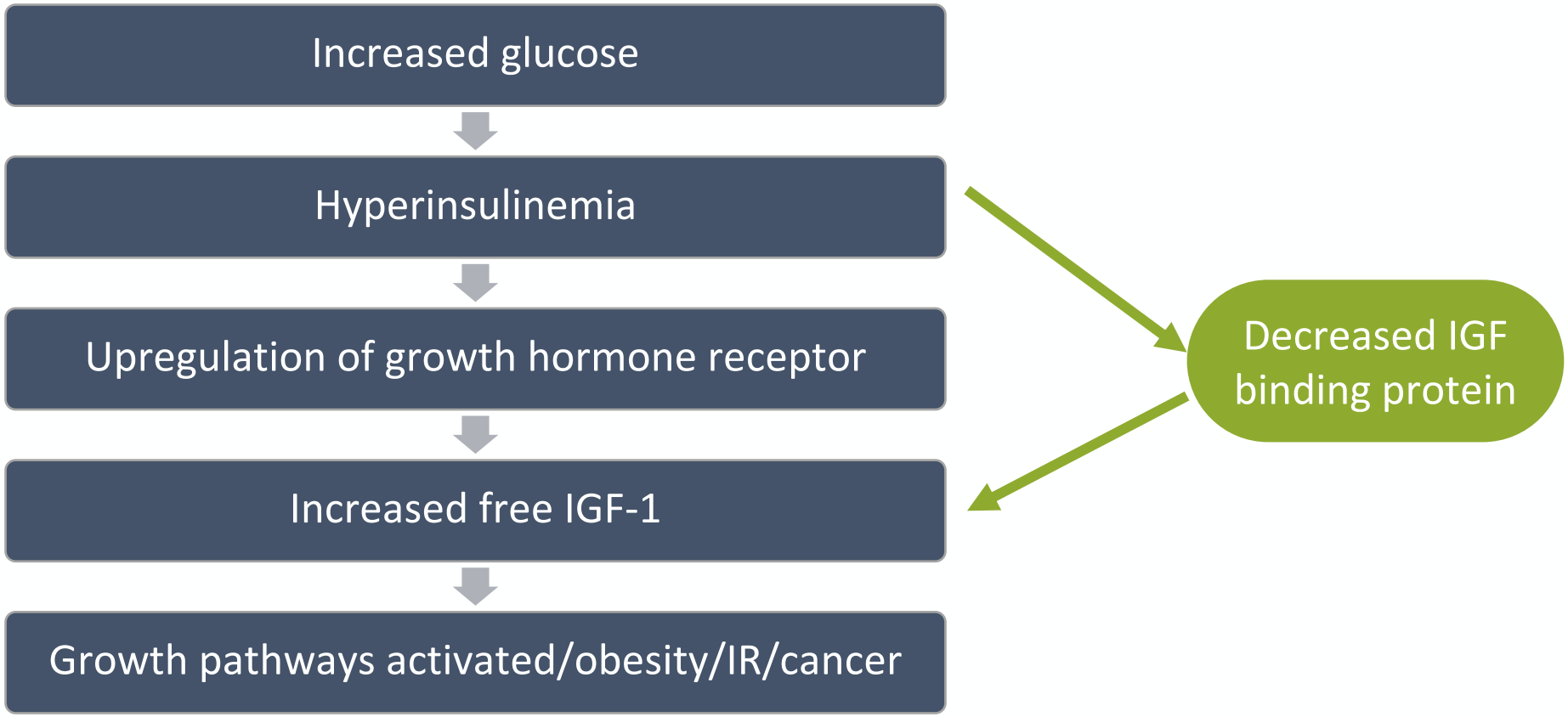
Mechanism of Fasting

What Happens When We Fast?



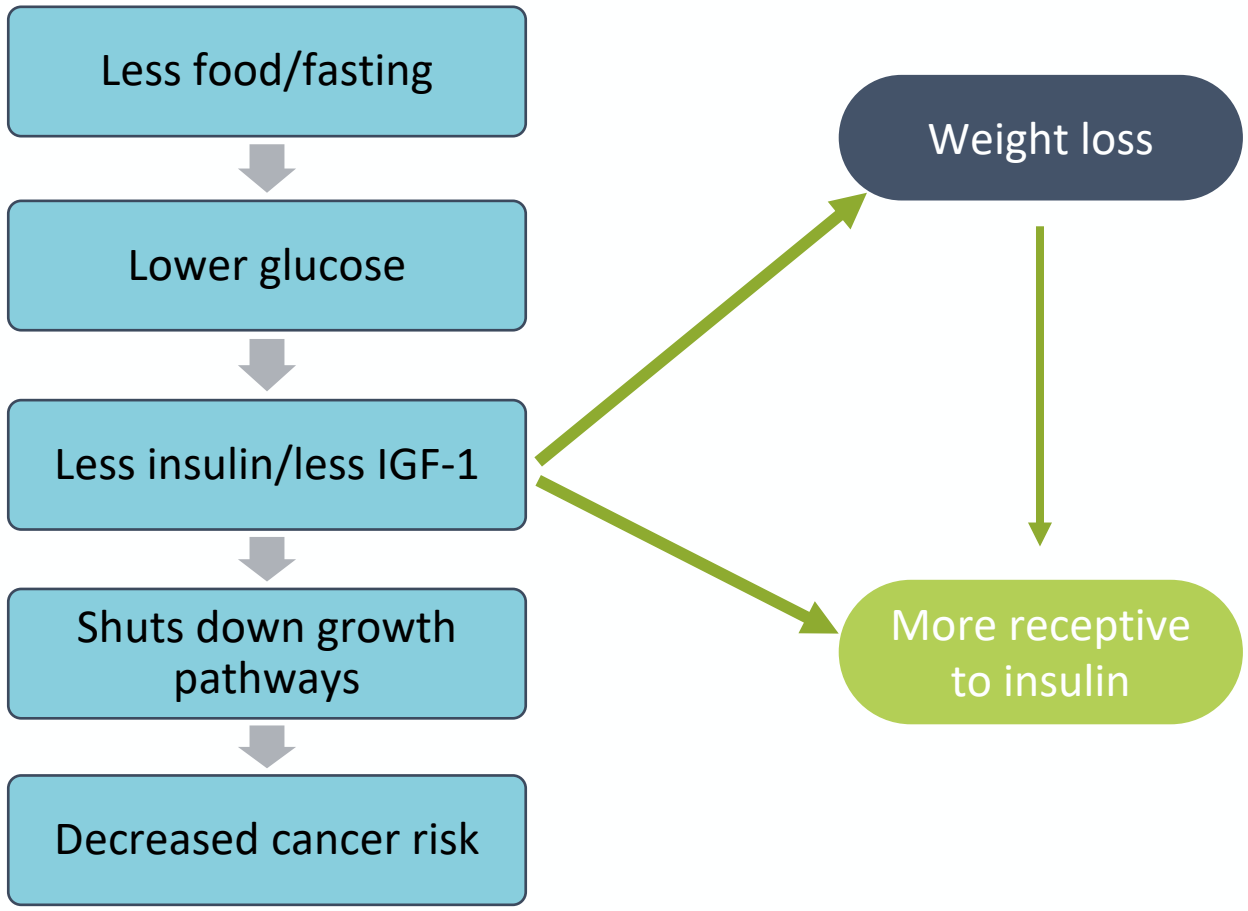
Longo VD, Mattson MP. *Cell Metab.* 2014

Cascade Effect from Excess Glucose/Energy Intake



Hursting SD, Dunlap SM, Ford NA et al. *Cancer Metab*. 2013

Fasting is Likely to Shut Down Growth Pathways, Improve Insulin Sensitivity



Hursting SD, Dunlap SM, Ford NA et al. *Cancer Metab*. 2013

Fasting is Not a Novel Approach

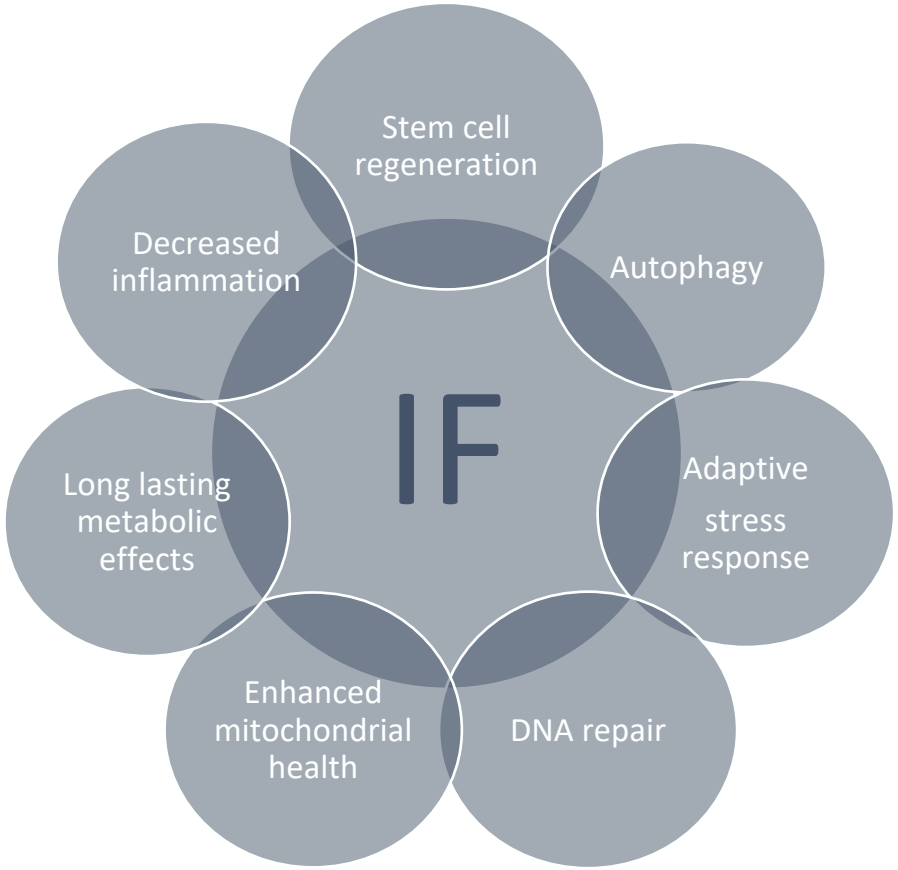
Ancestors lived off ketones in a fasted state

When Less is More: Fasting Physiology is Ingrained in Our Genome

- Nutrient deprivation increases longevity
- Primitive forms to complex, higher life forms
- Yeasts deprived of nutrients will arrest growth
- Repeated exposure to fasting: lasting adaptive, protective responses in mammals today

Longo VD, Mattson MP. *Cell Metab.* 2014

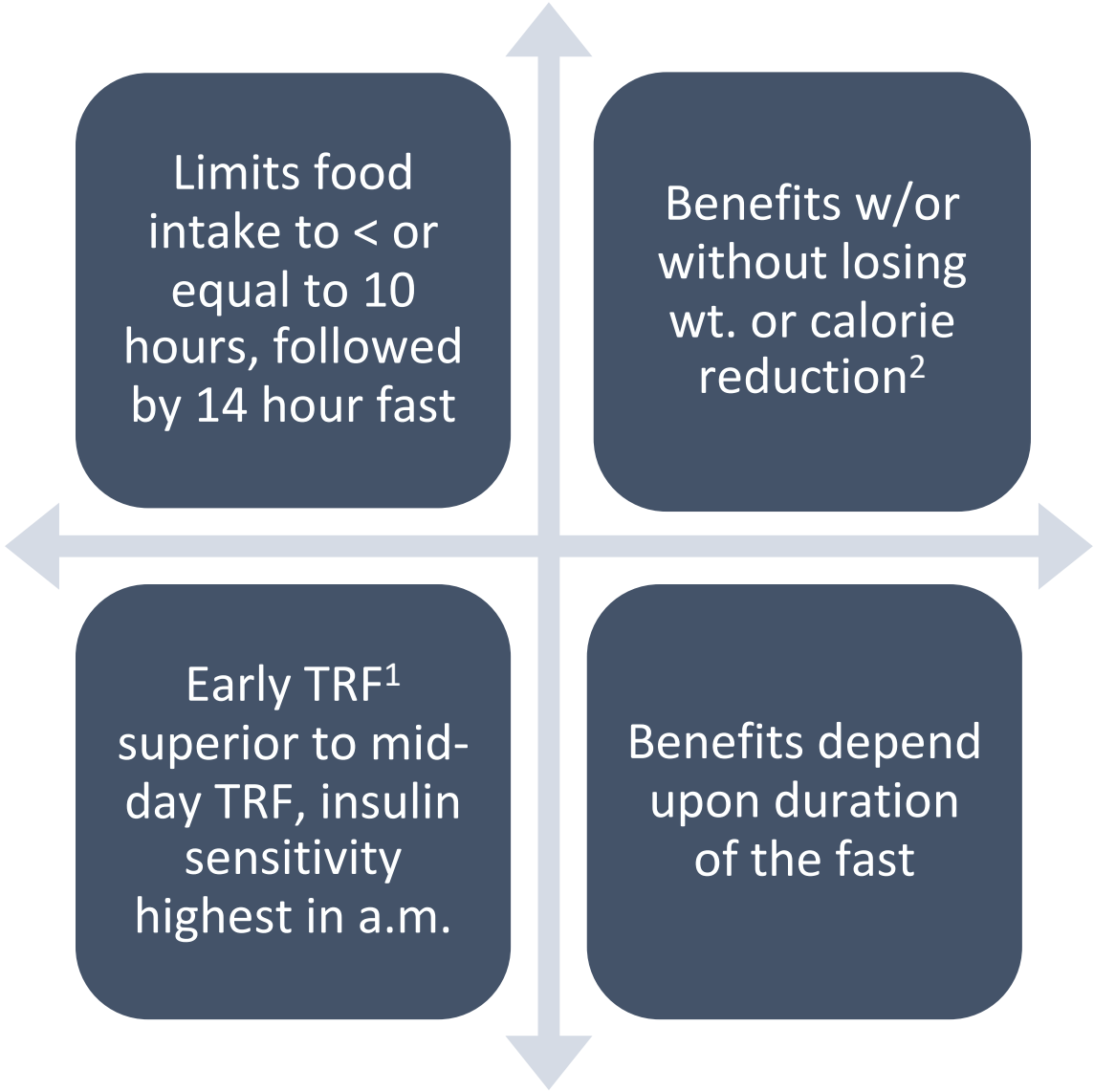
Intermittent Fasting (IF) and Calorie Restriction
Building the Cell's Arsenal



Antunes F, Erustes AG, Costa AJ, et al. *Clinics (Sao Paulo)* 2018
de Cabo R, Mattson MP. *NEJM, N Engl J Med* 2019

What is Time Restricted Feeding?

Human Studies



1. Xie, Z., Sun, Y., Ye, Y. et al. *Nat Commun*. 2022
2. Sutton EF, Beyl R, Early KS et al. *Cell Metab.* 2018

Time Restricted Feeding, or TRF

1. TRF is well-tolerated
2. May lead to an average of 20% unintentional reduction in caloric intake.
3. TRF may have additional benefits beyond calorie restriction:
    - Improves insulin sensitivity
    - Improves Metabolic markers
        - Systolic blood pressure, HbA1c, fat mass and triglycerides, even in calorie matched conditions
    - Better adherence, decreased appetite compared to simple calorie restriction

Adafer R, Messaadi W, Meddahi M, et al. *Nutrients*. 2020

What Do the Longer-Term Studies Show? (A Mixed Bag)

- The long-term efficacy and safety of TRF for wt. loss are not clear
- Randomized trial w/ 139 patients with obesity
- One group underwent TRF (eat between 8:00 a.m. and 4:00 p.m.) or daily calorie restriction alone x 12 months
- The primary outcome: change in weight from baseline
- 12 months was −8.0 kg in the TRF and −6.3 kg in the calorie-restricted group = statistically not significant
- Secondary outcomes: waist circumference, BMI, body fat, and measures of metabolic risk factors were not statistically significant
- TRF was not more beneficial than daily calorie restriction, but other studies have refuted this

Liu D, Huang Y, Huang C, et al. *N Engl J Med. 2022*.

RCT comparing e-TRF with M-TRF in Healthy, Non-Obese Folks

- 5-week RCT comparing eTRF (6 am-3 pm), with mTRF (11 am-8 pm), and a control (ad lib eating)
- Primary outcome: Greater insulin sensitivity in e-TRF vs m-TRF $p < 0.001$
- eTRF, but not mTRF:
  - Improved FBG, reduced total body and fat mass, decreased inflammation, increased gut microbial diversity
  - Improved metabolic outcomes could be related to circadian rhythms
  - First trial to show that eTRF is superior to mTRF by directly comparing the two
  - Several limitations: Sample size, non-blinded participants
    - The specific timing and duration of their meals varied within each group, which may skew results.
- In a 10 hr TRF x 12 weeks, (n=19), fat loss, improvement in lipids, A1C and BP seen in subjects with Metabolic syndrome

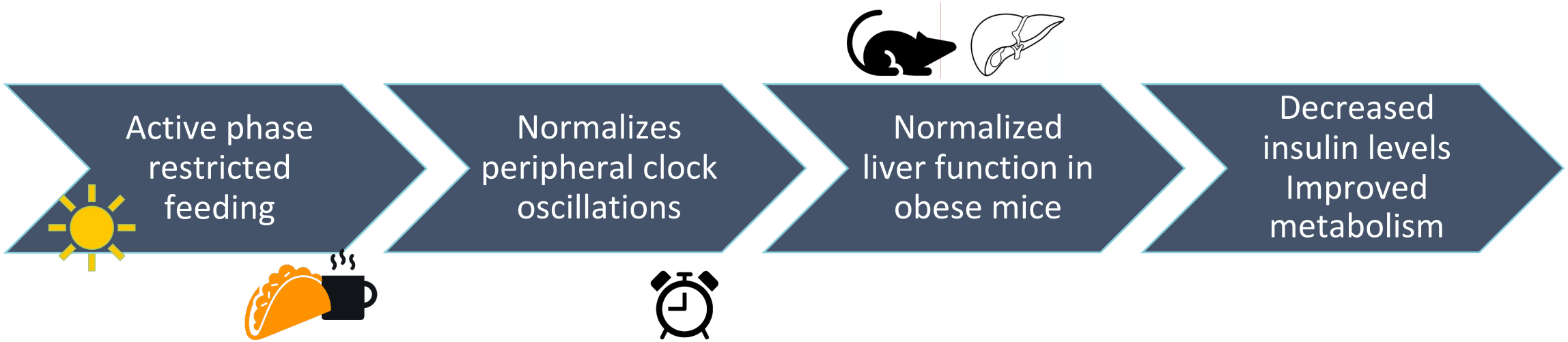
Xie, Z., Sun, Y., Ye, Y. *et al. Nat Commun* 2022
Wilkinson MJ, Manoogian ENC, Zadourian A, et al, *Cell Metab*. 2020

TRF and Circadian Rhythms

- Restores the primordial response in feed-fast cycle
- When limited to the **active** phase of the circadian cycle
- Diet-induced obesity dampens the daily feeding/fasting rhythm
- TRF restricted to the active phase partially restores these rhythms
- Corrects impaired clock gene expression from desynchronized feeding
- Resetting the circadian clock can lead to increased life span

Chaix A, Zarrinpar A, Miu P, Panda S. *Cell Metab*. 2014

TRF Entrains the Circadian System to Improve Cardiometabolic Parameters

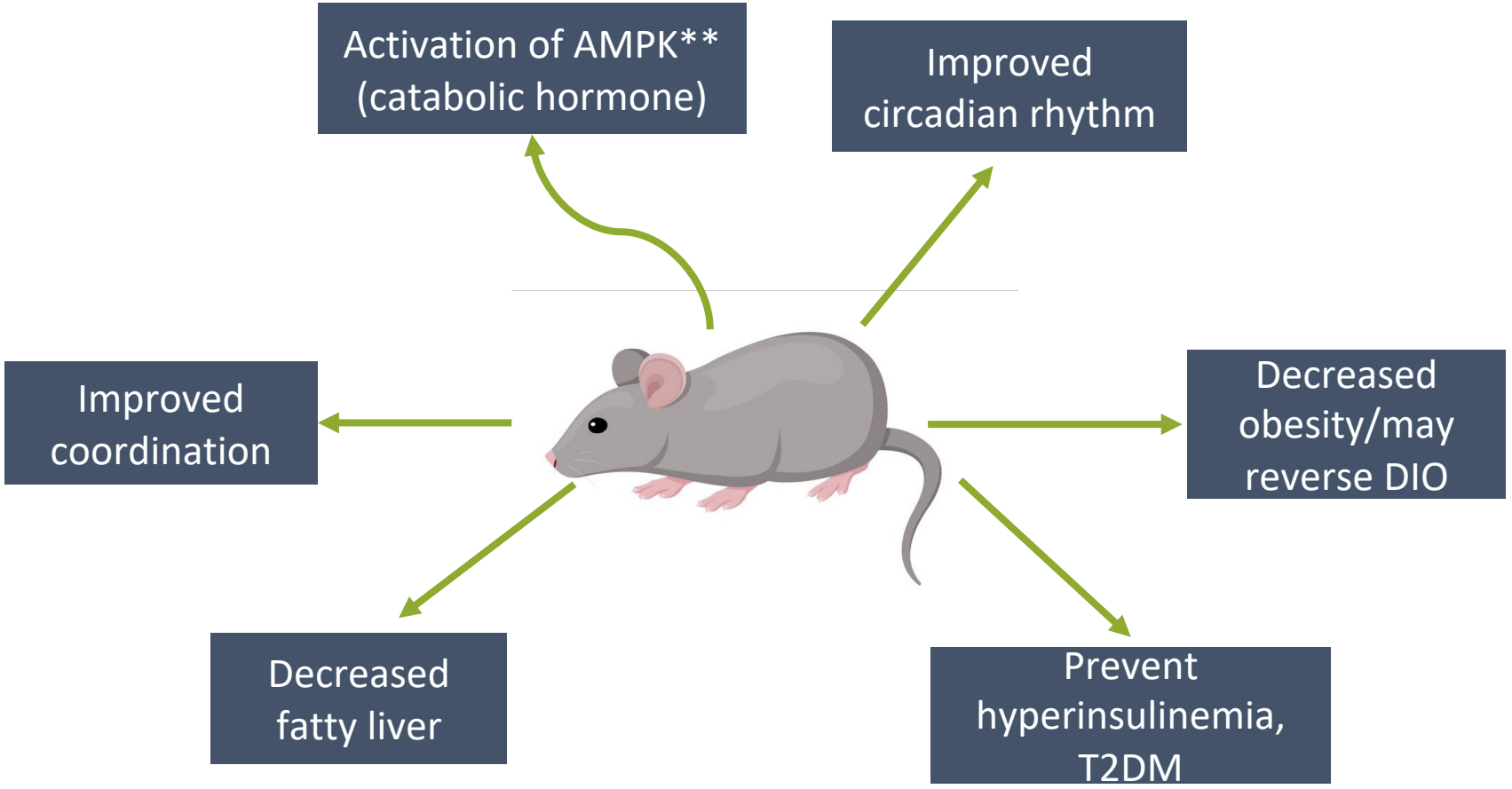


Sherman H, Genzer Y, Cohen R, Chapnik N et al. *FASEB J*. 2012

How Does Circadian Rhythm Disruption Cause Metabolic Disease?

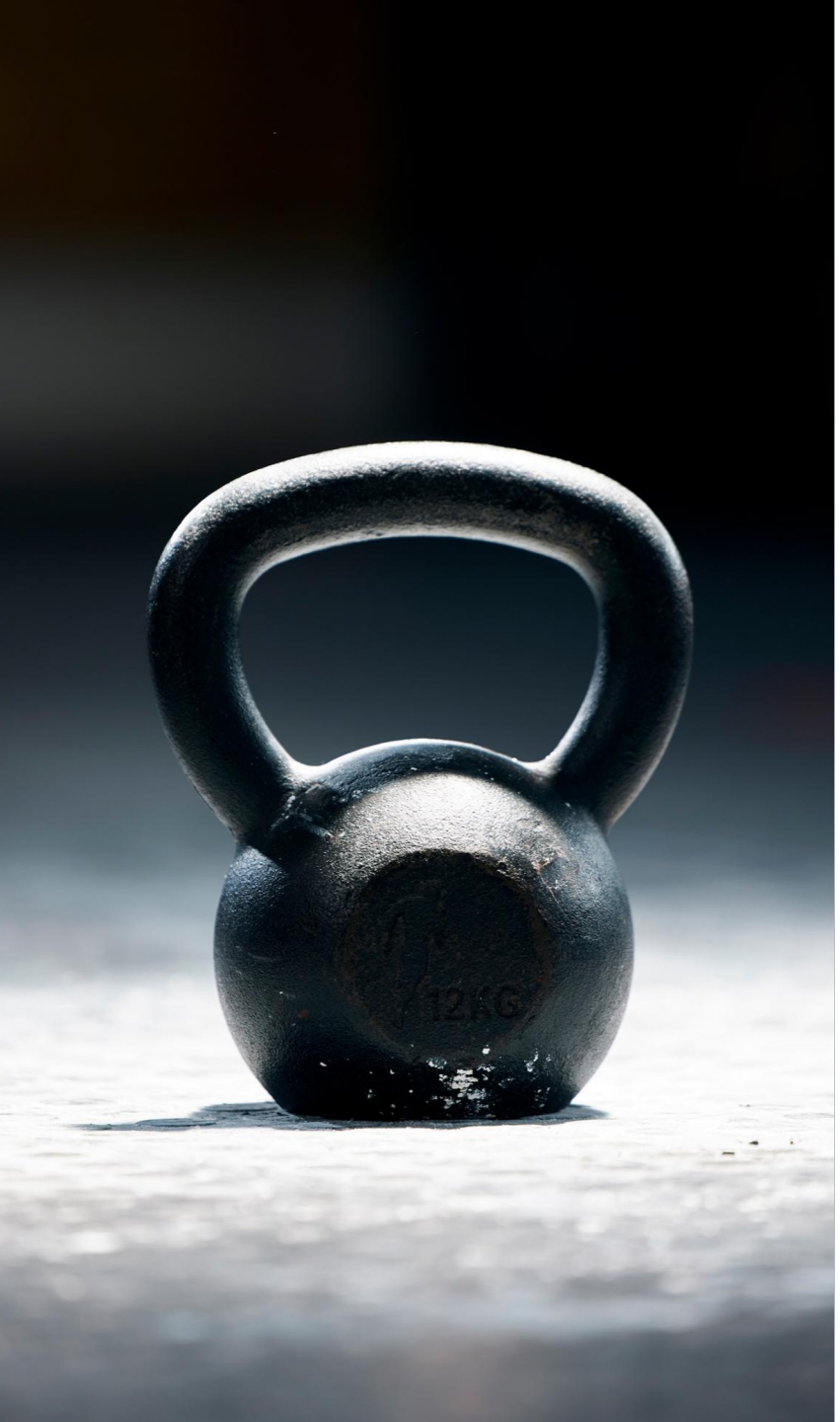
And, How Do We Mitigate This?

DIO* Dampens Rhythms: TRF Helps Prevent or Reverse Metabolic Disease



*DIO = Diet-induced obesity (usually from a high fat diet)
**AMPK = Adenosine Monophosphate-Activated Protein Kinase

Rothschild J, Hoddy KK, Jambazian P et al. *Nutr Rev*. 2014
Chaix A, Zarrinpar A, Miu P, Panda S. *Cell Metab*. 2014
Jakubowicz D, Barnea M, Wainstein J et al. *Obesity (Silver Spring)*. 2013
Gil-Lozano M, Mingomataj EL, Wu WK et al. *Diabetes*. 2014



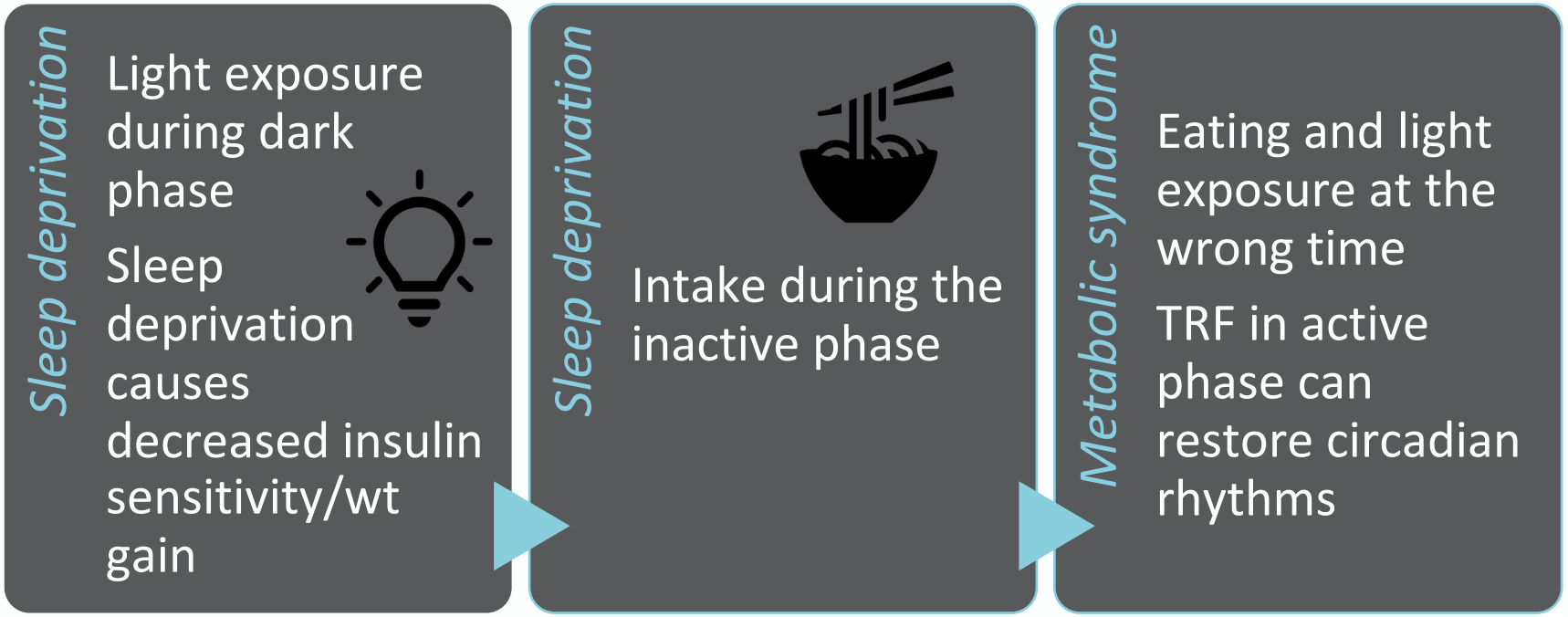
Poll Question

The best time to exercise from a circadian rhythm standpoint is:

A. Around 7-9 a.m.
B. 11 a.m.
C. 2 p.m.
D. 5 p.m.

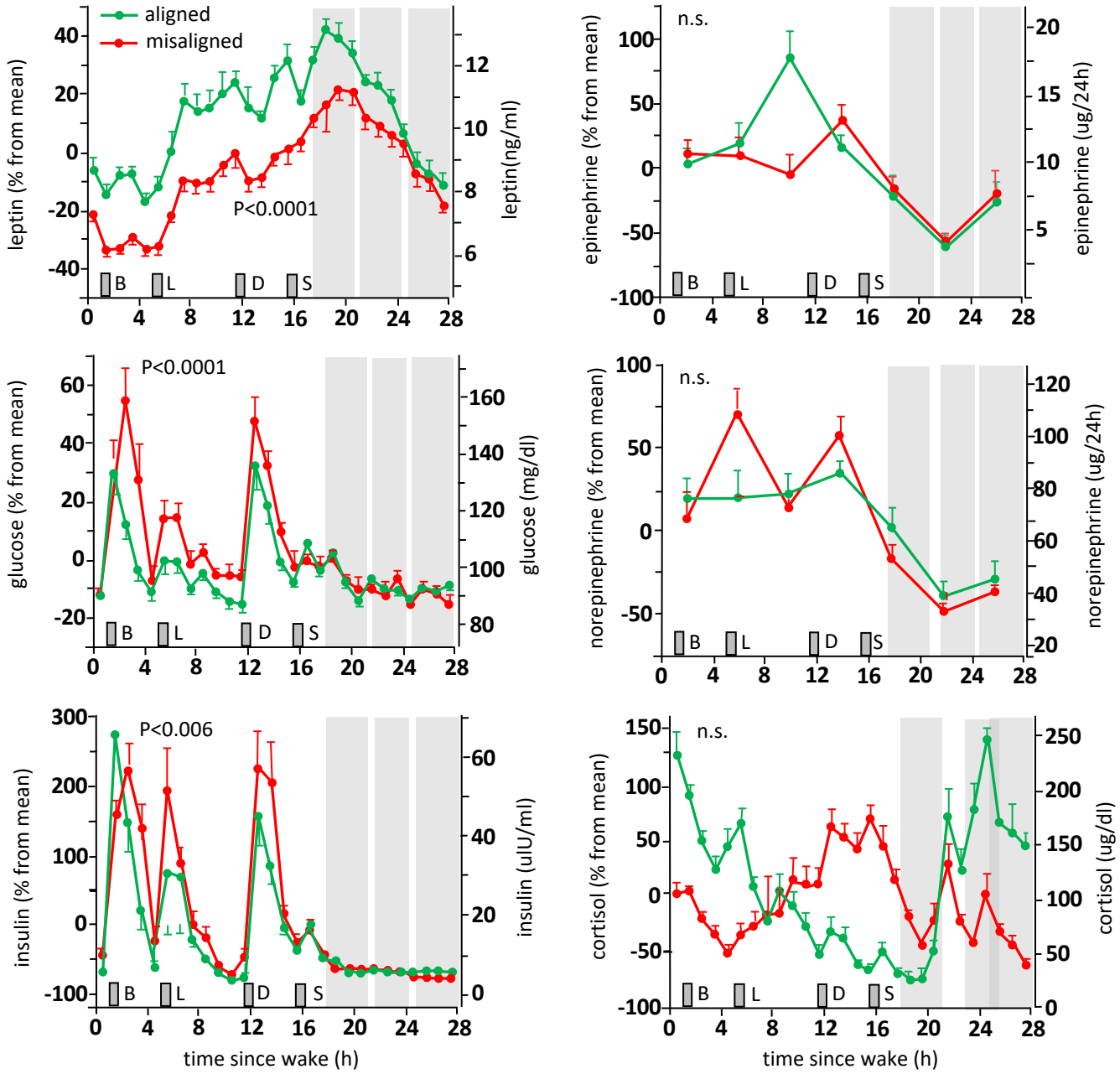
What's Common Between Shift Work and Jet Lag?

What we do when we're awake at the wrong time, matters



Fonken LK, Workman JL, Walton JC, et al. *Proc Natl Acad Sci U S A*.
Pickel L, Sung HK. *Front Nutr*. 2020

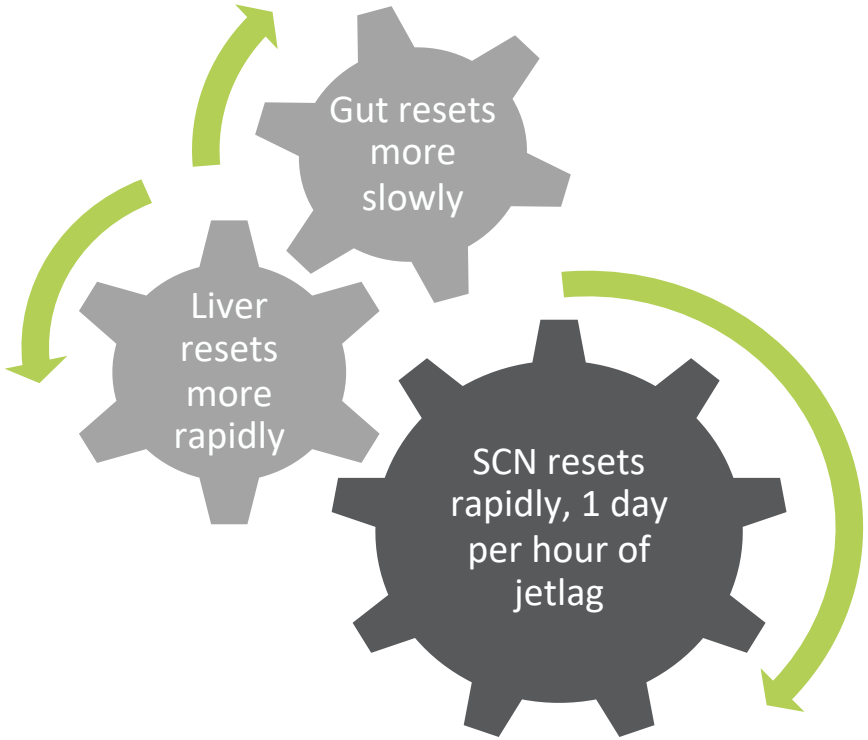
Consequences of Circadian Misalignment on Metabolic, Autonomic, and Endocrine Function



Adapted from: Frank A. J. L. Scheer et al. PNAS 2009;106:11:4453-4458

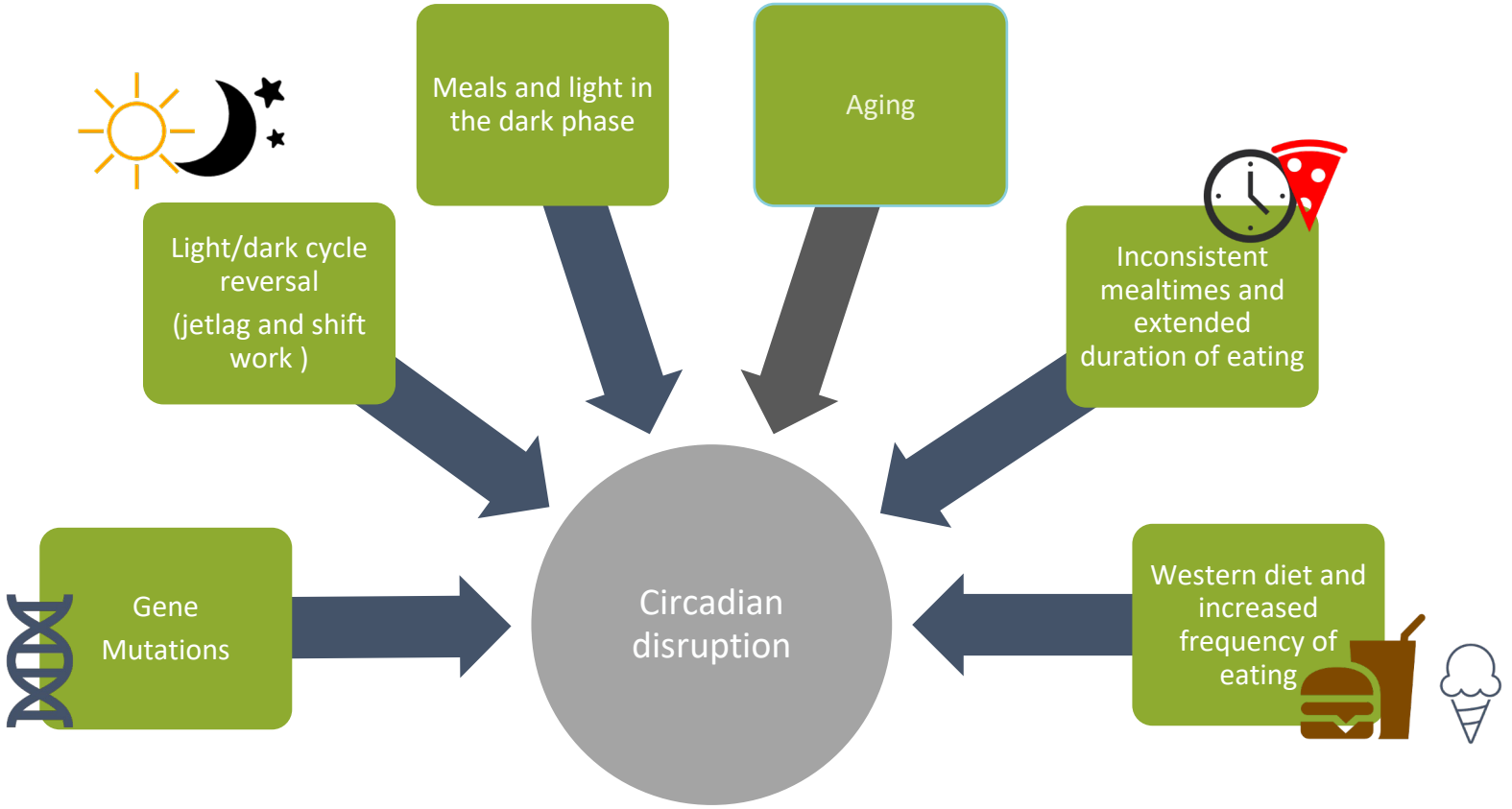
Jet Lag and Shift in Peripheral Clocks in Rest Phase Feeding

In response to a change in the light/dark (LD) cycle, intrinsic clocks reset at varying rates causing desynchrony

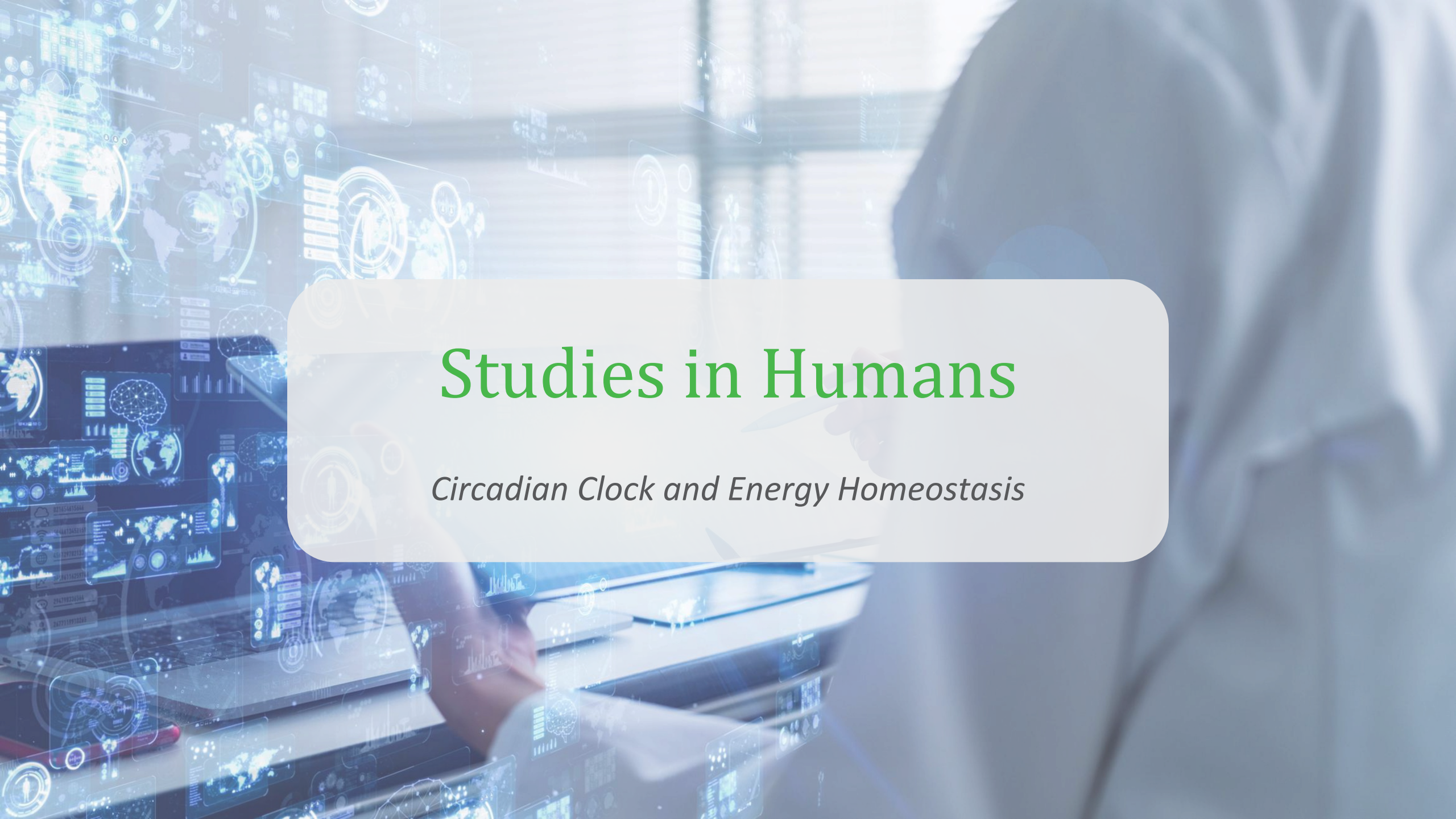


Common Circadian Disrupters

Some of these cause an altered microbiota



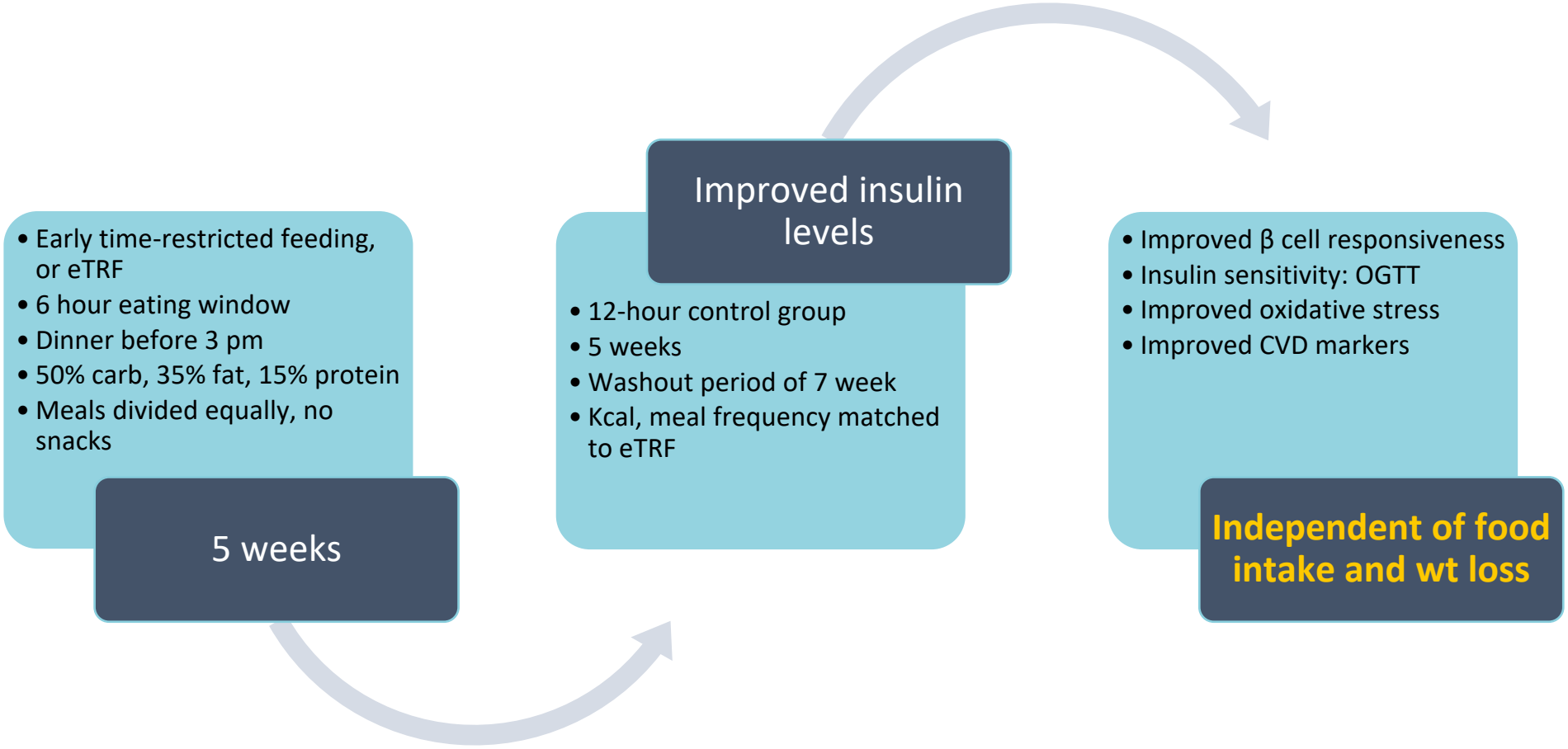
Pickel L, Sung HK. *Front Nutr*. 2020



Studies in Humans

Circadian Clock and Energy Homeostasis

First Rigorous RCT in Men with Prediabetes
Combining IF with Circadian Rhythms - eTRF



Sutton EF, Beyl R, Early KS. *Cell metabolism,* 2018

Impact of High-Energy Breakfast (B-diet) on Glucose Levels

- In a randomized, crossover design, 18 individuals with T2D treated with metformin and/or diet were given either Bdiet or Ddiet* for 7 days.
- High energy intake at breakfast (Bdiet) was associated with significant reduction in overall PPBG in diabetic patients over the entire day compared to the reverse diet (Ddiet)

*Ddiet = low energy breakfast and high energy dinner

Jakubowicz, D., Wainstein, J., Ahrén, B. et al. *Diabetologia*. 2015

Bdiet: A Useful Tool Against Obesity and Metabolic Syndrome?

- **Objective:** Compare a weight loss diet with high caloric intake during breakfast to an isocaloric diet with high caloric intake at dinner
- **Design and methods:** Overweight and obese women (with metabolic syndrome) were randomized into two isocaloric (~1400 kcal) weight loss groups, x 12 weeks
- **Results: Both groups lost weight, however, in the BF group:**
  - Greater weight loss and waist circumference reduction
  - Significant decrease in fasting glucose, insulin, and HOMA-IR
  - Mean TGs decreased by 33.6% in the BF group but increased by 14.6% in the D group
  - Insulin, ghrelin, and mean hunger scores were significantly lower, whereas mean satiety scores were significantly higher in the BF group

Jakubowicz D, Barnea M, Wainstein J et al. *Obesity (Silver Spring)*. 2013

Circadian Variations in the Energy Expenditure and Metabolic Pattern of Healthy Individuals

- Twenty healthy subjects were enrolled in an RCT
- Randomly received the same standard meal in the morning and, 7 days after, in the evening, or vice versa
- RMR significantly increased after the morning meal ($P<0.001$)
- Delayed and larger increases in glucose and insulin concentrations after the evening meals for the same meal

Bo S, Fadda M, Castiglione A, et al. *Obes (Lond)*. 2015

A Few Pooled Studies:

Authors	Year of publication	Participants	Main finding	Ref. no.
Sakai et al.[37]	2018	Men and women Type 2 diabetics	Late-night dinner independently associated with poor glycaemic control	37
Kajiyama et al.[49]	2018	Young women Healthy	Late-night dinners increased postprandial hyperglycaemia Consuming dinner dividedly ameliorate postprandial glucose levels	49
Imai et al.[51]	2017	Men and women Type 2 diabetics	Late-night dinners increased postprandial hyperglycaemia	51
Van Cauter et al.[46]	1992	Men and women Healthy	For identical mixed meals, total and 2-h AUC were 25–50% greater in the evening than in the morning	46
Jakubowicz et al.[57]	2013	Women Overweight and obese metabolic syndrome (BMI: 32 kg/m^2)	High-energy breakfast and reduced-energy dinner significantly reduces postprandial glycaemia in obese non-diabetic individuals	57
Jakubowicz et al.[53]	2015	Men and women Type 2 diabetics	High-energy breakfast and reduced-energy dinner significantly lowered postprandial glycaemia	

Henry, C.J., Kaur, B. & Quek, R.Y.C. *Nutr. Diabetes*, 2020

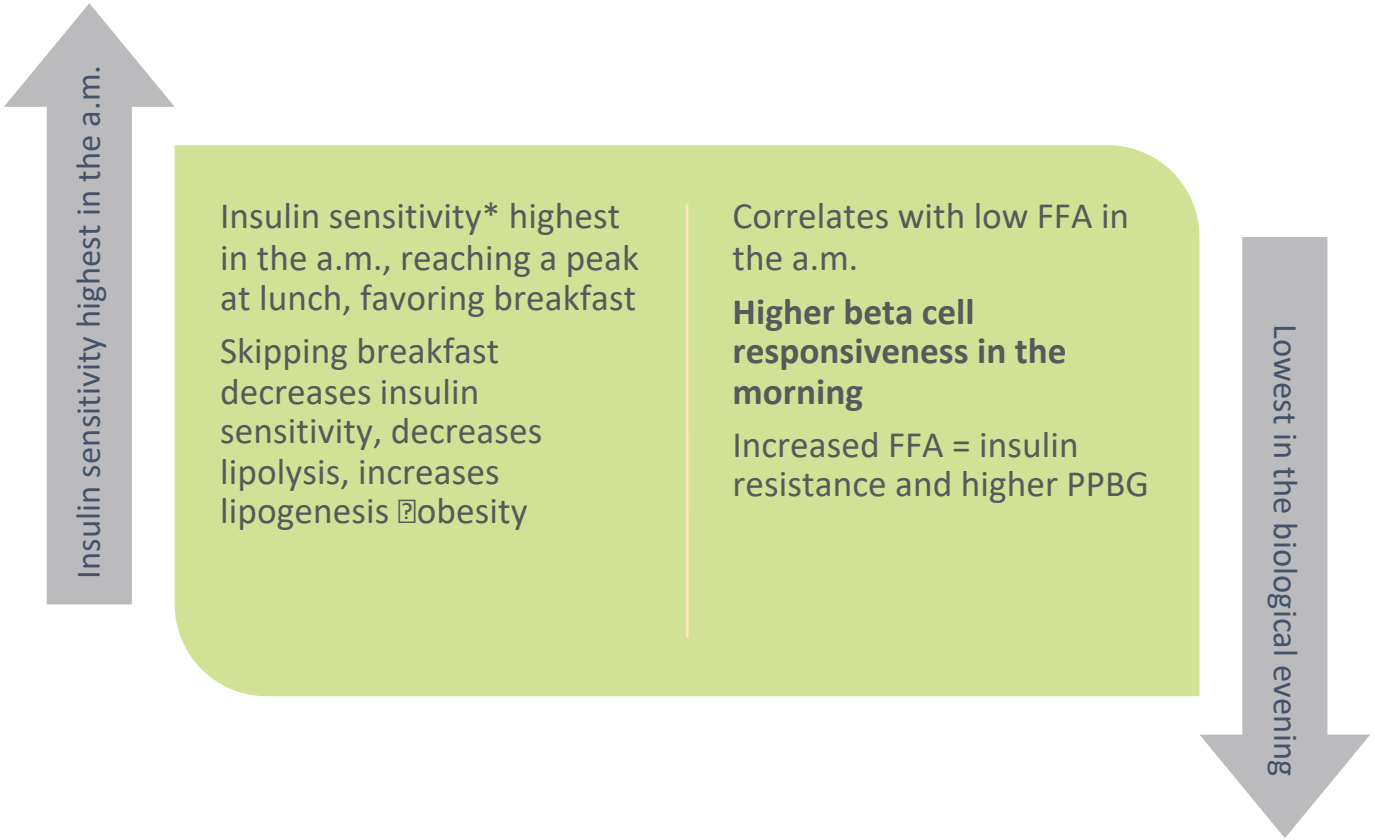
What Do the Pooled Studies Tell Us ?

- Skipping breakfast strongly correlates with IR (insulin resistance) and T2DM[1]
- In patients w/T2DM, who were later chronotypes and skipped breakfast, higher A1c values seen
- Results were independent of age, sex, race, BMI, number of diabetes complications, insulin use, depressive symptoms, perceived sleep debt, and percentage of daily caloric intake at dinner

1. Reutrakul S, Hood MM, Crowley SJ et al. *Chronobiol Int*. 2014

Summary of Glucose Metabolism

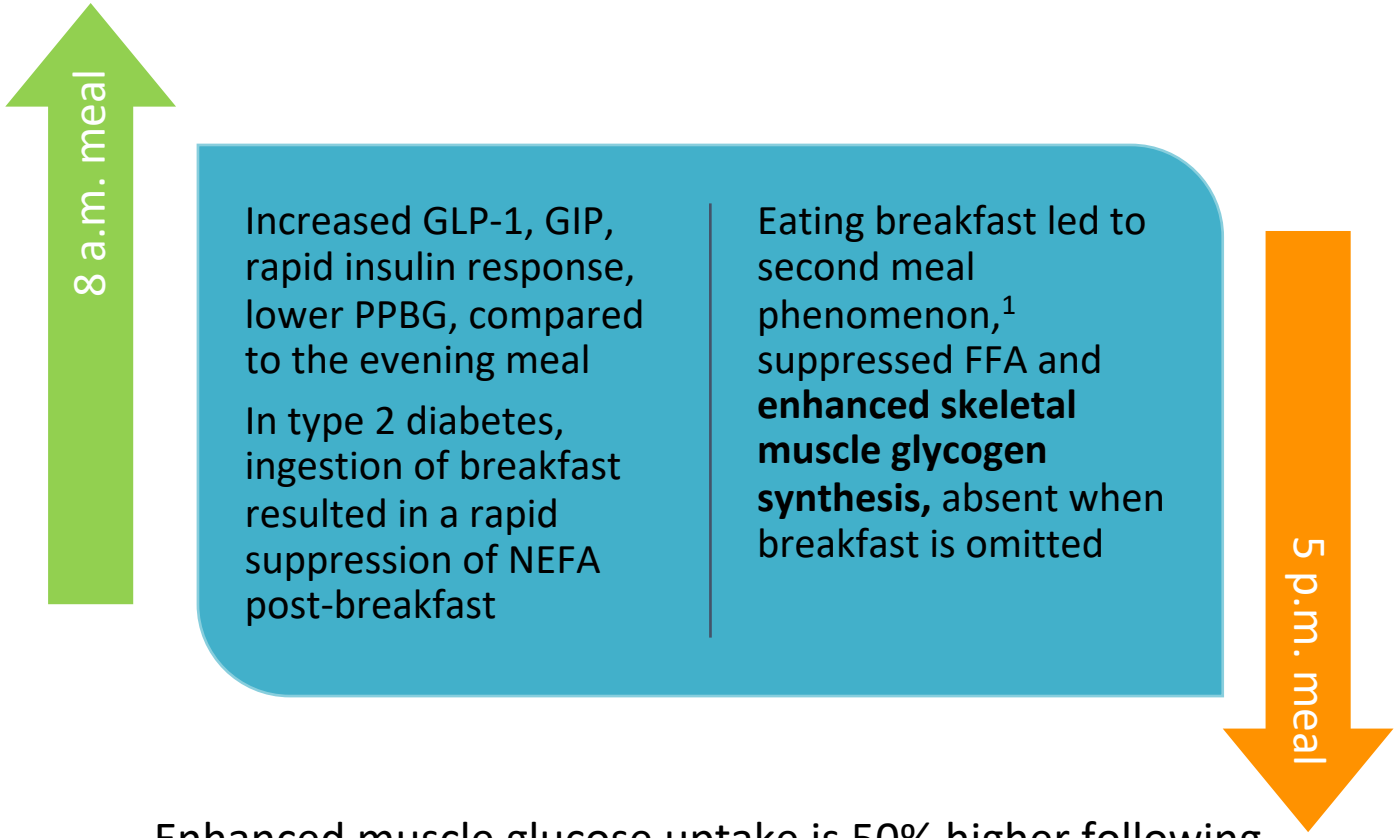
Comparing Isocaloric Meals of Identical Macronutrient Composition Consumed at 8 a.m. and 5 p.m.



*in subcutaneous tissue

Reutrakul S, Hood MM, Crowley SJ et al. *Chronobiol Int*. 2014

What is the Second Meal Phenomenon?



NEFA = non esterified fatty acids
FFA = free fatty acids
GLP 1= glucagon like peptide1
GIP = gastro-intestinal peptide

Enhanced muscle glucose uptake is 50% higher following breakfast compared to when breakfast is skipped

Jovanovic A, Gerrard J, Taylor R. *Diabetes Care*. 2009

What is Chrono-Nutrition?

Could obesity be characterized as a chrono-biological disease?

Chrono-Nutrition: Align Food Intake with Circadian Rhythms

- Chrono-nutrition aligns food intake with times when circadian rhythms are optimized for nutrition
- It encompasses meal timing, frequency, and distribution, not just nutrient value
- Shift meal patterns to earlier in the day
- Including **breakfast** has a legacy effect, lowers blood sugars later in the day, increases lipolysis[1]
- Eating a carbohydrate-rich meal at night results in increased postprandial glycemia compared with an **identical** meal in the morning
- A crossover study in healthy participants showed a high protein meal tempered the glucose response at night[2]
- Meal *timing* has crucial implications on weight gain, appetite, and glucose and lipid metabolism

1. Jovanovic A, Gerrard J, Taylor R. *Diabetes Care*. 2009
2. Davis R, Bonham MP, Nguo K et al. *Clin Nutr*. 2020

Chrono-Nutrition Continued...

In an RCT w/ 13 healthy adults, thermal effect of food (thermogenesis), in the morning was 44% higher than in the evening [1,2]

Rate of gastric emptying is higher at 8 a.m. vs 8 p.m. [3]

Could be translated to public health advocacy efforts in communities with T2DM, dependent on a high carbohydrate diet

1. Henry, C.J., Kaur, B. & Quek, R.Y.C. *Diabetes* **10,** 6 (2020).
2. Morris CJ, Yang JN, Garcia JI, et al. *Obesity (Silver Spring)*. 2015
3. Hoogerwerf WA. *Am J Physiol Gastrointest Liver Physiol*. 2010

What's Your Chronotype:

Night Owl or Early Bird?

- Chrono-nutrition is influenced by an individual's "chronotype"
- Chronotype is related to an individual's internal clock
  - Helps classify if they prefer the morning or evening
- Individuals with "later chronotype" are biologically driven to consume foods later in the day, often skip breakfast, wake up and sleep late
- Later chronotype linked with metabolic syndrome, increased diabetes risk and poorer glycemic control in T2D patients

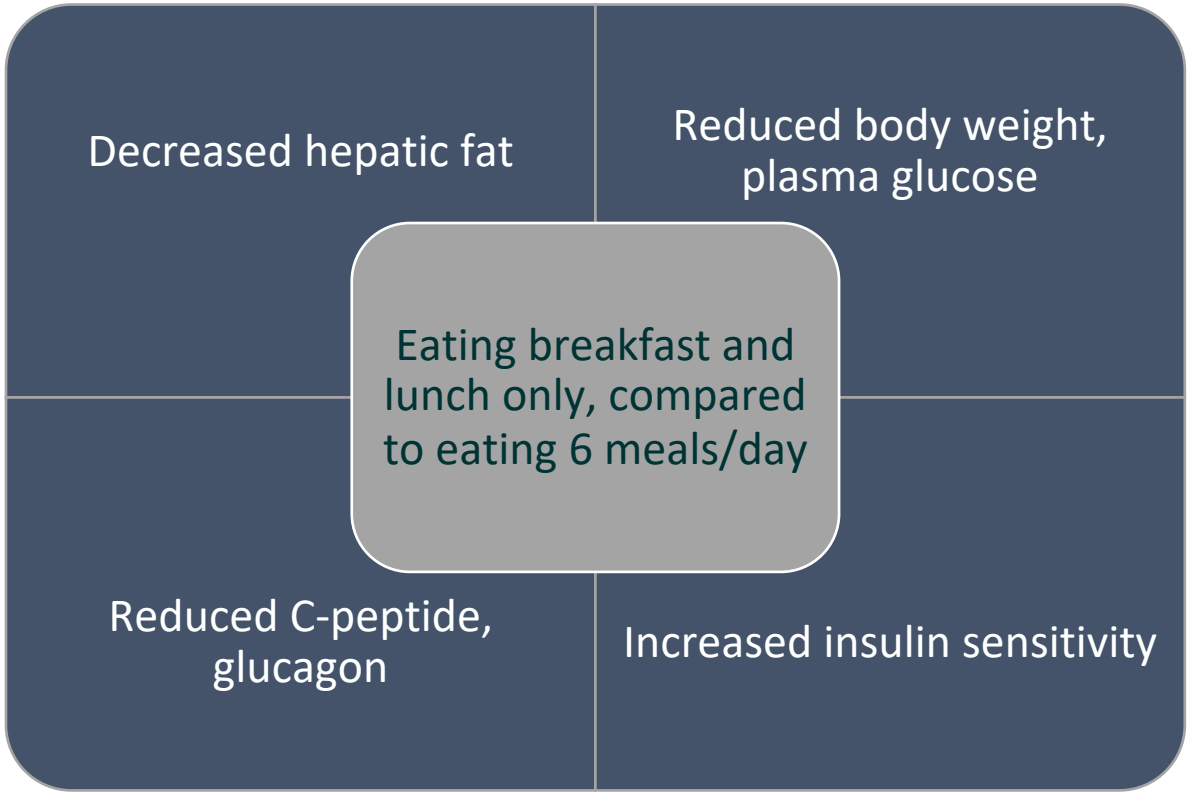
Reutrakul S, Hood MM, Crowley SJ et al. *Chronobiol Int*. 2014

Case Study 1

- Mrs. A is a 61-year-old Caucasian woman, recently diagnosed with metabolic syndrome
- Her diet recall:
  - She tells you she goes to bed late and routinely skips breakfast
  - Lunch is mostly a store-bought salad with 4 oz grilled chicken or sometimes she has a sandwich with 3 oz deli meat , with a bag of chips
  - She tries to eat some fruit or yogurt around 4 p.m. but tells you her “hunger is out of control” by dinner time
  - She eats an enormous meal at 5:30 p.m. but starts nibbling at 8:30 p.m. for at least ½ an hour or more
- Her FBG has ticked up to 140 mg/dl and she has gained 15 lbs over the last 2 years
- Her pre-lunch blood sugars are also elevated
- What’s Mrs. A’s chronotype? What would be your advice to her, and why?

Two Large vs Several Small Meals in Patients w/ T2D

- 24-week randomized, cross-over trial[1]
- 54 patients w/ T2D
- 2 regimens, 12 weeks each
  - Breakfast and lunch only vs
  - 6 meals a day
- Both regimens had the same macronutrient and energy content
- Larger scale, long-term studies needed before offering recommendations re: meal frequency
- Benefits attributed to increased fasting period vs meal frequency[2]



1. Kahleova H, Belinova L, Malinska H, et al. *Diabetologia*. 2014
2. Pickel L, Sung HK. *Front Nutr*. 2020

Glucose and Insulin Response Show a Diurnal Variation in Healthy Individuals and in T2D

- The PPBG after the high-energy breakfast was significantly lower than after the low-energy breakfast
- Carb tolerance decreases toward the evening in identical meals, in healthy folks and those with type 2 diabetes[1-3]
- Attributed to rapid, early prandial GLP-1 level with increased beta cell function in the am
- GLP-1 secreted by the L-cells of the gut show a circadian rhythm with increased insulin release after the first meal [1,4]

1. Jakubowicz D, Barnea M, Wainstein J et al. *Obesity (Silver Spring)*. 2013;
2. Morgan LM, Shi JW, Hampton SM etal. *British Journal of Nutrition*. 2012
3. Gibbs M, Harrington D, Starkey S et al. *Clin Nutr* 2014
4. Gil-Lozano M, Mingomataj etal. EL, Wu WK *Diabetes*. 2014;63(11):3674-3685. doi:10.2337/db13-1501

Later Eating Leads to Greater Eating??

- Hunger peaks in the evening
- The same caloric intake in a different time window during the day led to a different body weight
- Consuming > 1/3 of total kcals after 5 p.m. doubles obesity risk
  - Worsens lipid and glucose profiles
- The **majority** of energy distribution across the **first** two meals of the day lead to favorable health outcomes

Kahleova H, Belinova L, Malinska H, et al. *Diabetologia*. 2014
Pickel L, Sung HK. *Front Nutr*. 2020

Lessons from the Clock:

- The clock genes drives key metabolic pathways in the body
- Clock disruption leads to cardiometabolic disease and potentially cancer
- Circadian rhythms persist in the absence of external cues
- Meal timings reset peripheral clocks, **overriding signals by the SCN**
- TRF in the active phase, restores metabolic homeostasis
- Chrono-nutrition realigns normal circadian rhythms, has therapeutic potential for treating endocrine-related disorders
- Translating this knowledge to clinical practice is still limited
- **Long term studies in human beings are needed**

Listen to Your Clock: Take Home Messages for Patients

- Light is a universal time giver
- Get plenty of sunlight especially in the *early* a.m. to fully activate the central clock
- This will release adequate cortisol for physical and mental alertness
- Exercise in the *late afternoon* primes muscle for activity and can offset disruptive sleep patterns
- Dim the lights *an hour or so before* bedtime and switch off blue light emitting devices to allow a robust melatonin onset
- Eat within the “light-phase” of the clock and preferably within a 10-12 hour eating window
- This mobilizes all the right circadian genes, hormones, and enzymes to support homeostasis and a strong circadian rhythm

Practice Guidelines

- Timed feeding patterns may reduce cardiometabolic risk via *both* fasting and circadian mechanisms
- Discuss why a bigger breakfast (vs a skimpy one) is key (legacy effect)
  - GLP-1, beta cell responsiveness and increased muscle glucose uptake in the am
- Encourage patients to consume most of their calories at breakfast and lunch, with a lighter dinner
  - Increased am thermogenesis (body “wastes” kcals) vs lower thermogenesis in the pm
- Decline in carbohydrate tolerance toward the evening means a higher carb meal at breakfast and a slightly higher protein meal at dinner is beneficial
- Align feeding/sleep cycles to the clock in the new time zone for jet lag as soon as possible
- Feeding should coincide with the active phase of the clock for shift work

You Are When You Eat!

- The circadian system is an intricate, precisely timed mechanism
- It works like clockwork when we are aligned to the biological day
- A robust circadian system is like a beautiful symphony
- However, it is very plastic, and our modern lifestyles can easily break these age-old clocks and turn the symphony to a discordant cacophony
- Many patients experience a mismatch between their endogenous clocks and socially-dictated behaviors
- Let’s help our patients synchronize their behaviors to their circadian clocks
- The circadian clock could be tomorrow’s therapeutic target for metabolic syndrome/weight/sleep disorders
- Timing is everything!
- A symphony, not a cacophony!

Questions?

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