Circadian Clocks, Metabolism and Disease

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The Use of Biology and Energy Drinks Workshop
August 15, 2013

America’s top 7 favorite energy drinks

PRODUCT (8 fluid oz)	Calories	Sugars (g)	Caffeine (mg)
1. Red Bull Energy Drink	105	26	79
2. Monster Energy	100	27	92
3. Rockstar Energy Drink Double	140	31	80
4. NOS High Performance Energy Drink	110	26	112
5. Amp Energy	110	29	71
6. Full Throttle	220	58	210
7. Xylence Xenergy	0	0	94

24/7 Wallst.com, Posted March 25, 2013

Consumer Reports magazine (December 2012)

Caffeine and increased caloric intake alters circadian clocks.

- Chronic caffeine consumption lengthens the period of circadian locomotor rhythms in mice and alters clock gene expression.
  Oike et al., *Biochem Biophys Res Commun*. 2011

- Diet-induced obesity is a key risk factor for a variety of chronic conditions, including diabetes, hypertension, high cholesterol, stoke, cardiovascular disease and cancer.
  Alberti et al., Circulation, 2009

- Poor-quality sleep is associated with elevated BMI and development of metabolic disorders.
  Van Cauter et al., Eur J Endorinol, 2008

Outline

I. Overview of circadian rhythms and core clock machinery

II. Integration of circadian rhythms and metabolism

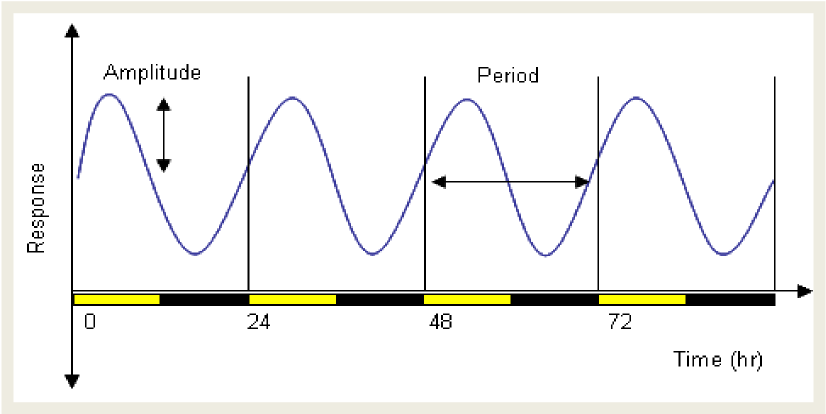
III. Circadian disruption and disease

IV. Role of the circadian system in metabolism
   a. Glucose metabolism and insulin secretion
   b. Molecular control of Sirt1 and NAD: impact on mitochondrial oxidative metabolism
   c. Impact of high fat diet on circadian rhythm: differential effects of saturated and unsaturated fatty acids

I. Circadian Rhythms

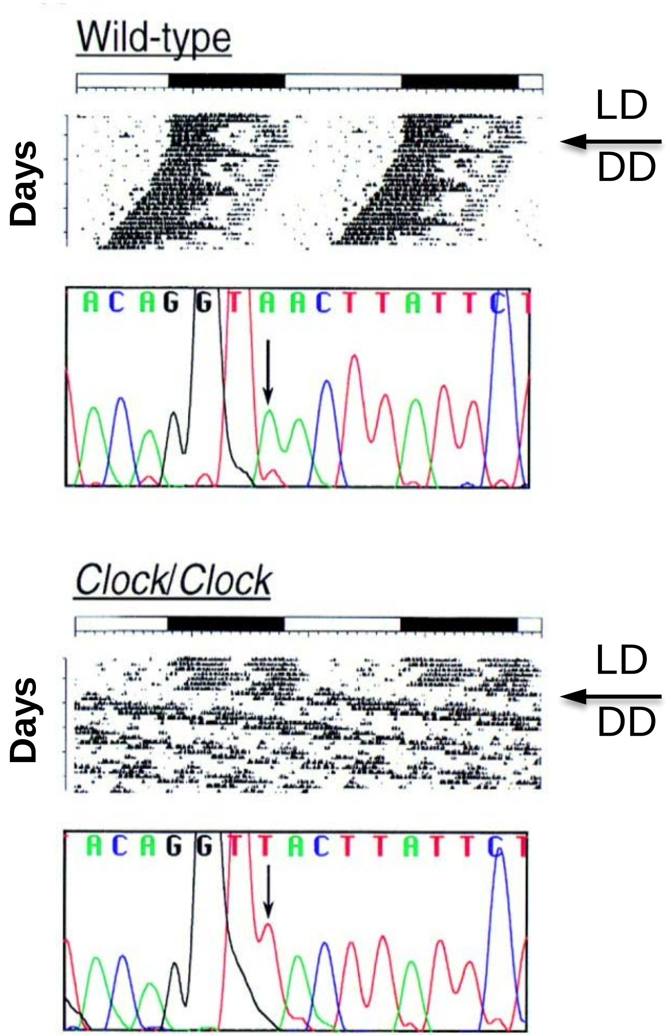
- Derived from Latin ‘circa diem’ (about a day)
- Defined as a biological rhythm that persists under constant conditions with a period length of ~24 hrs
- Mammalian circadian clock orchestrates the synchronization of the daily behavioral and physiological rhythms to better adapt the organism to the external environment

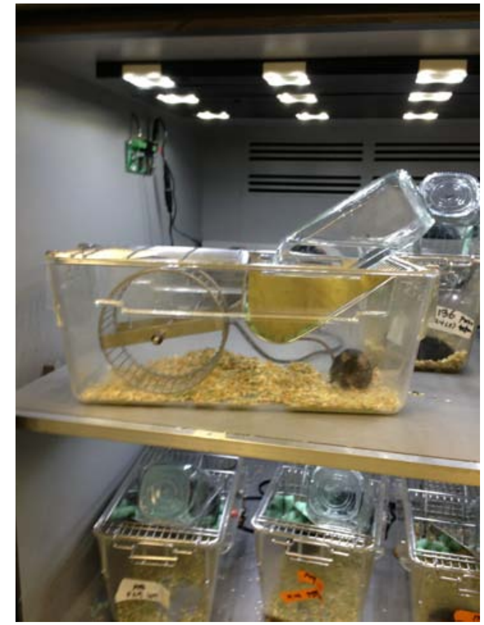
Sleep ⇄ Wake



Feeding

Genetic Basis of Timing



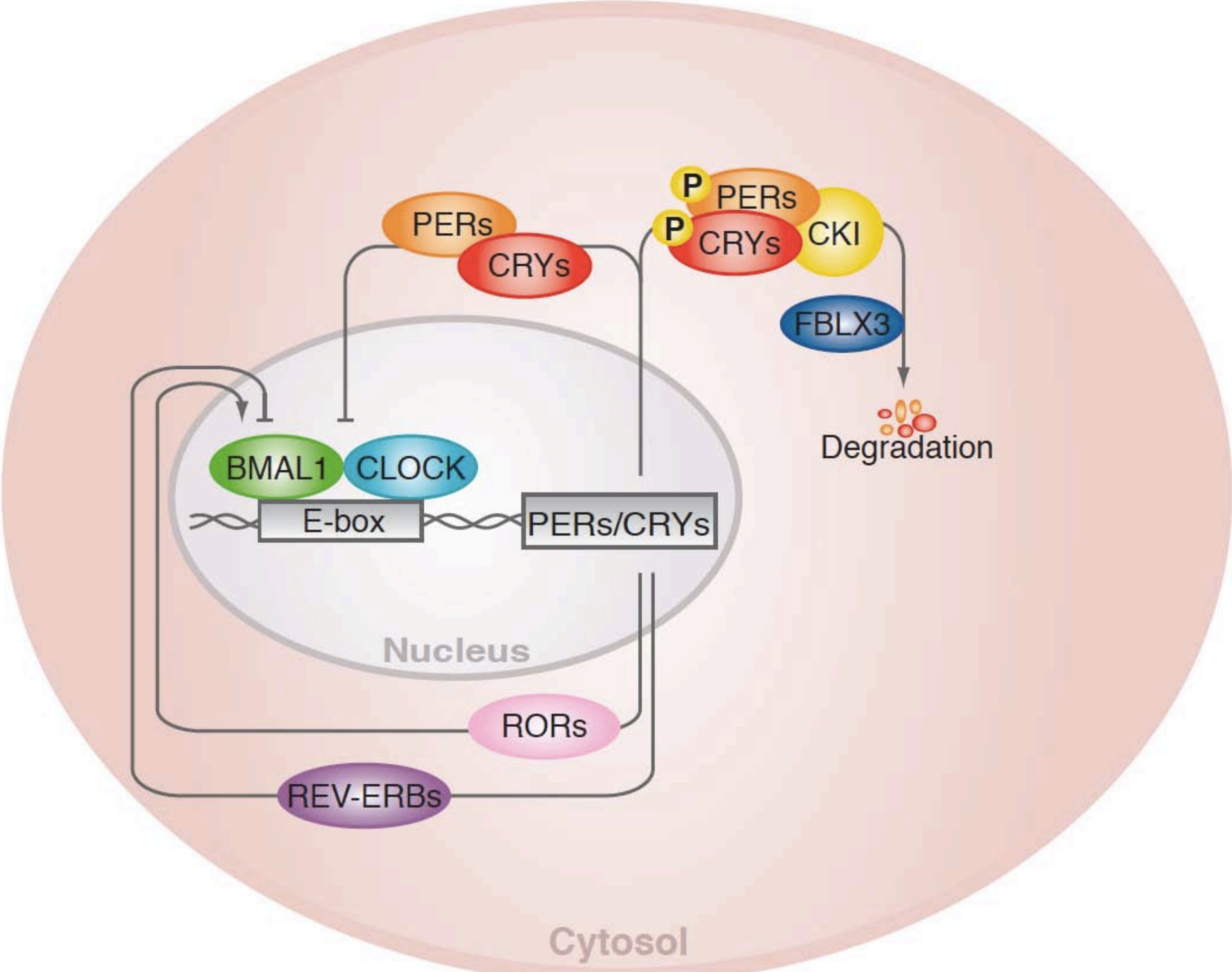


Vitaterna et al., *Science*, 1994
King et al., *Cell*, 1997

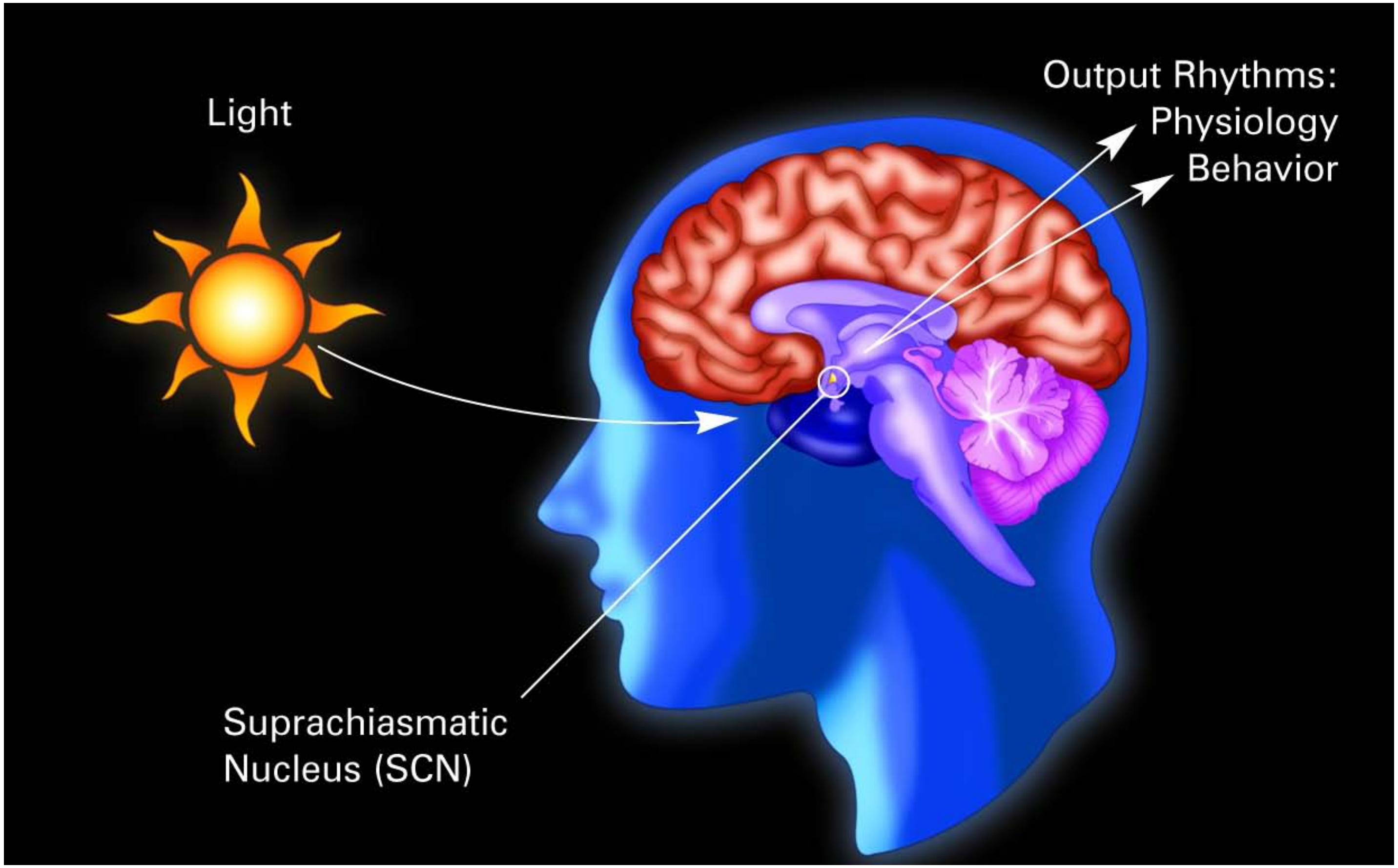
Clock Mutation Results in Loss of Behavioral Rhythms

- *Clock* mouse was identified in an ENU mutagenesis screen
- Light/Dark cues are sufficient to maintain activity rhythms in *Clock* mice
- Free running behavior rhythms are lost

Mammalian circadian clock is composed of a cell autonomous transcriptional-translational feedback network

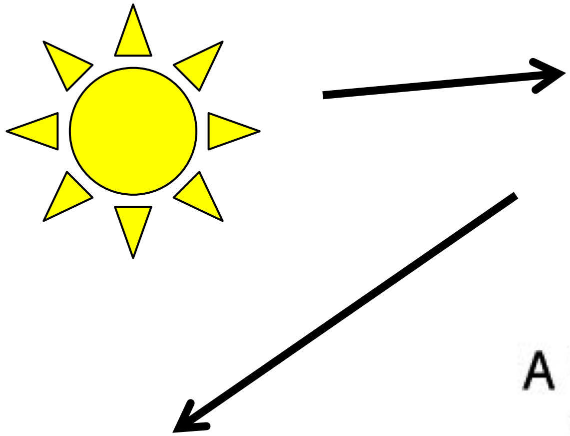


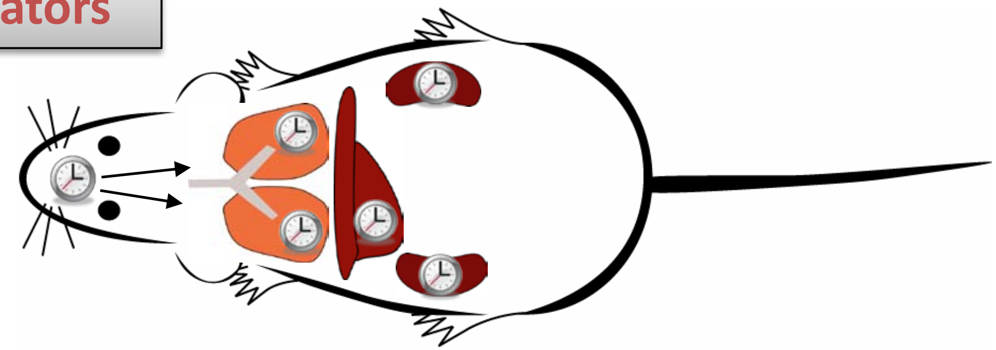
Mammalian Circadian Pacemaker



National Institute of General Medical Sciences

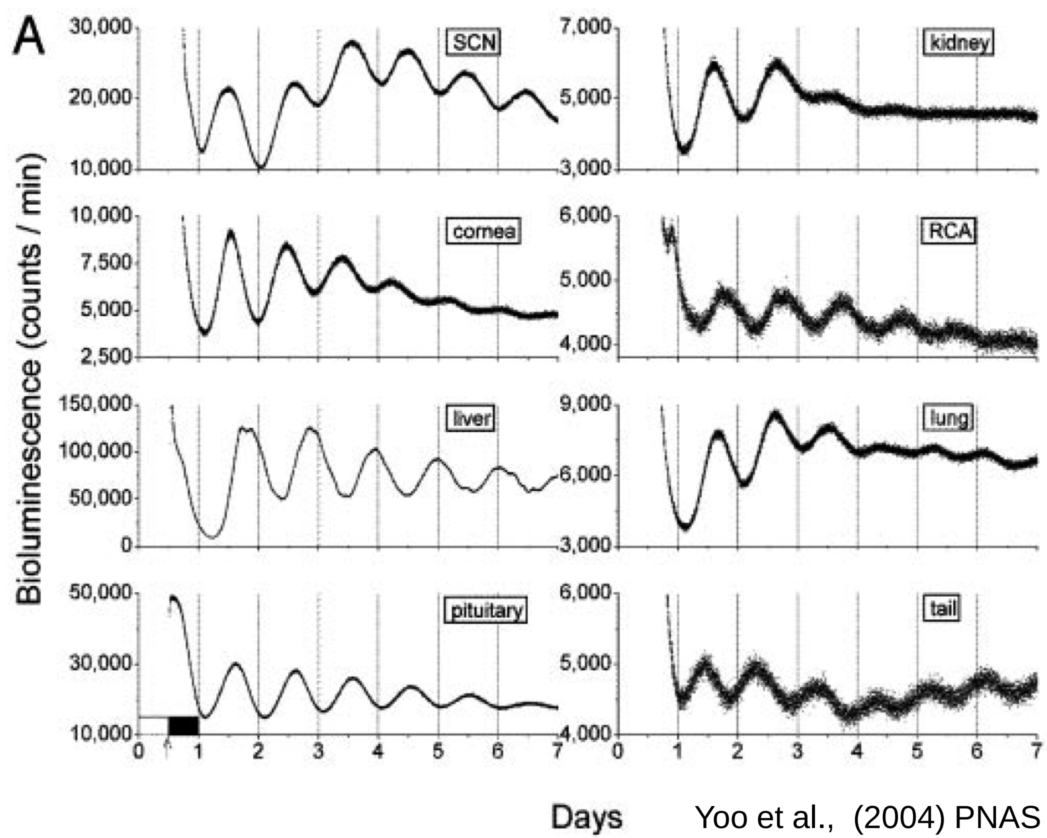
Central vs. Peripheral (local) Oscillators





- Sleep/Activity
- Thermoregulation
- Food consumption
- Blood pressure
- Hormonal release
- Metabolism

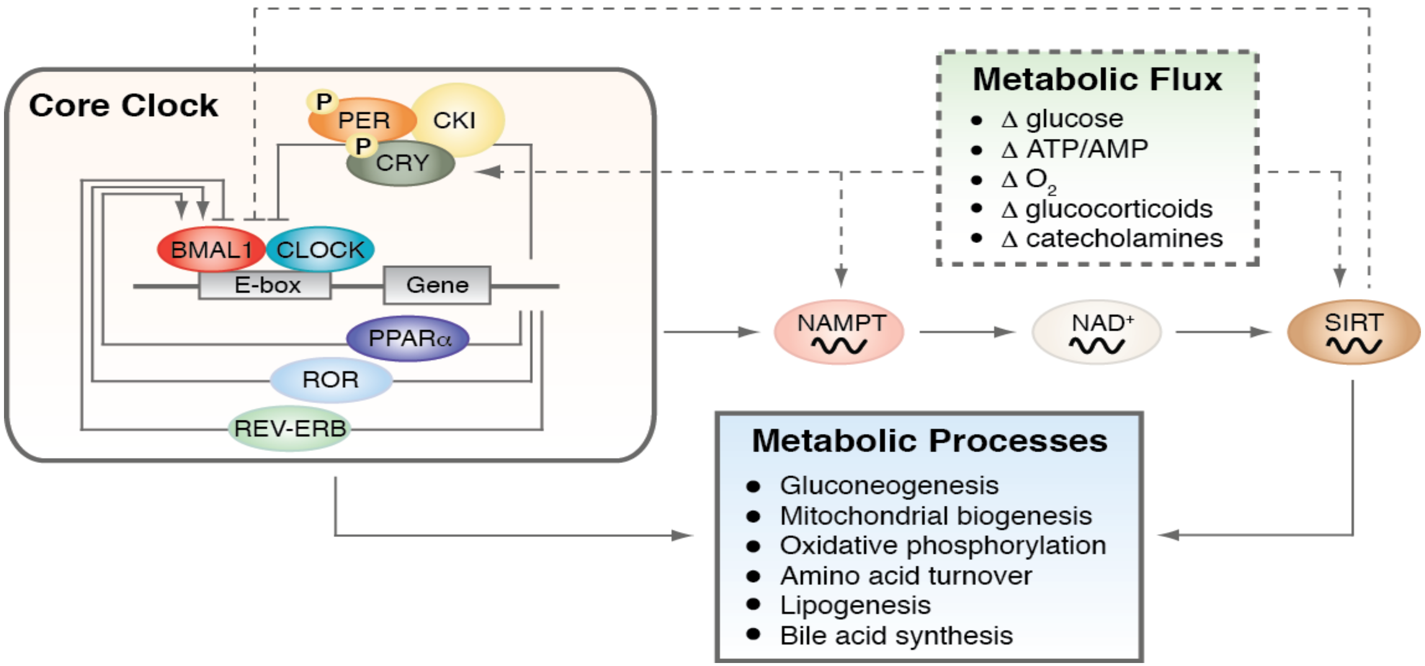
Per2::Luciferase Rhythm



Yoo et al., (2004) PNAS

Circadian Rhythms and Glucose Metabolism in Humans

- Blood glucose levels peak at the onset of the active period
  Arslanian et al, Horm Res, 1990; Bolli et al, Diabetes, 1984
- Glucose tolerance is impaired in evening compared to morning hours
  Gagliardino et al, Chronobiologia, 1984
- Decreased insulin secretion and altered insulin sensitivity in the evening
  Boden et al, Am J Physiol, 1996
- Daily cycles of insulin secretion and sensitivity are lost in diabetic patients
  Boden et al, Diabetes, 1999



II. *Clock* Mutants Provide Genetic Evidence Linking Circadian Rhythmicity and Metabolism

WT ***Clock***

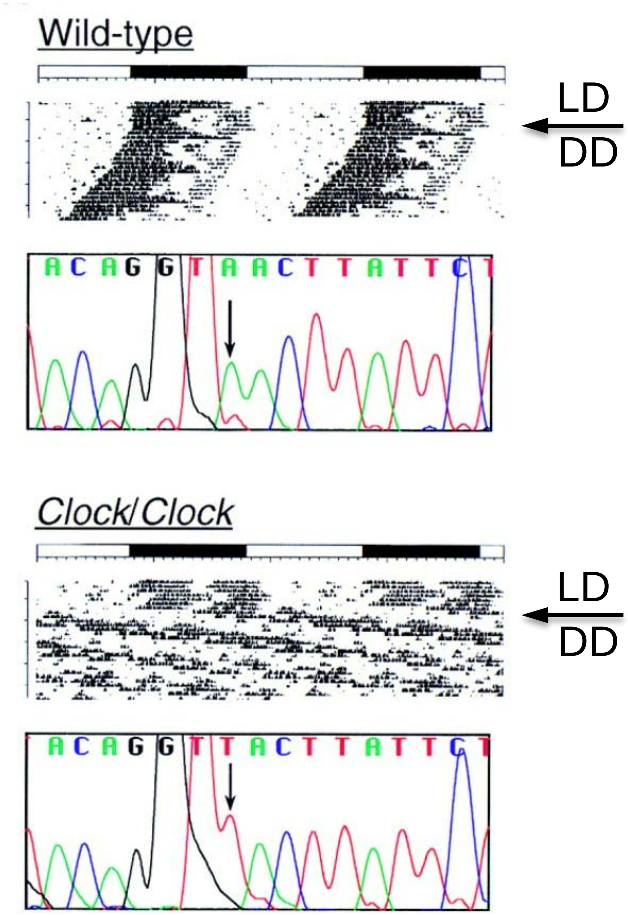
- Hyperdipidemia
- Susceptible to diet-induced obesity
- Age-dependent hyperglycemia
- Hypoinsulinemia at young age

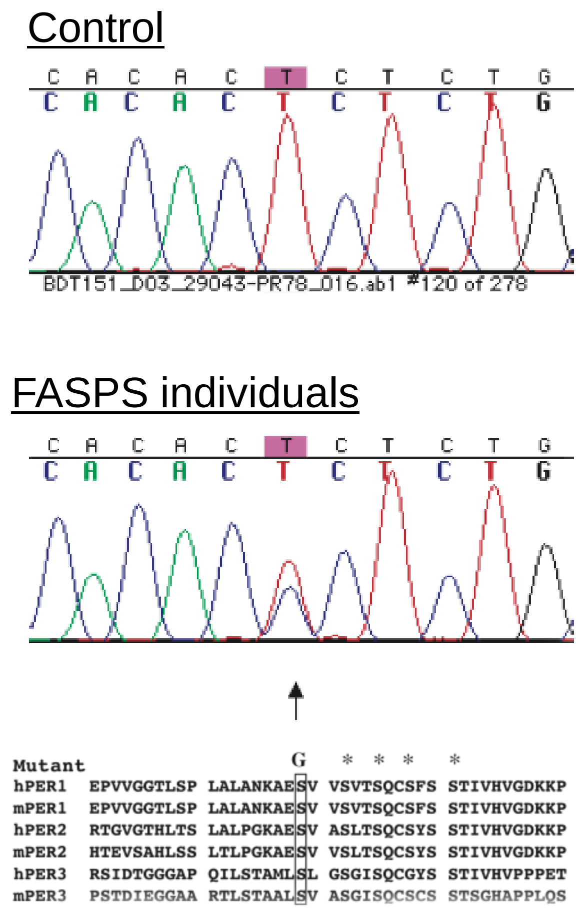
Turek et al, *Science*, 2005

III. Circadian Mutations and Metabolic Disease (mouse studies)

Whole Body Mutation	Circadian Phenotype	Cardiometabolic Phenotype	Reference
Clock $^{\Delta 19/\Delta 19}$	Arrhythmic	Age-dependent hyperphagia, obesity, hyperlipidemia, hyperglycemia, hypoinsulinemia, reduced muscle strength, endothelial dysfunction	PMID 11163178, 8171325, 20956306, 20562852, 15845877, 19273720
Bmal1 $^{-/-}$	Arrhythmic	Loss of glucose and triglyceride oscillations, increased insulin sensitivity, hypoinsulinemia, increased vascular stiffness, thrombosis, endothelial dysfunction, age-associated dilated cardiomyopathy, reduced muscle strength	PMID 22707558, 20829506, 20956306, 20562852, 15523558, 19273720
Per1 $^{-/-}$	Arrhythmic	Impaired glucocorticoid rhythm	PMID 11389837, 16505983
Per2 $^{-/-}$	Arrhythmic	Aortic endothelial dysfunction	PMID 11389837, 17404161
Per1/Per2/Per3 $^{-/-}$		Increased vascular stiffness	PMID 20829506
Cry1/Cry2 $^{-/-}$	Arrhythmic	Salt-sensitive hypertension	PMID 10217146, 20023637
Per2/Cry1 $^{-/-}$		Loss of ACTH and glucocorticoid rhythm	PMID 16890544
Rev-erb$\alpha^{-/-}$		Impaired bile acid synthesis, hepatic steatosis	PMID 19721697, 21393543
Rev-erbα/*Rev-erb*$\beta^{-/-}$	Arrhythmic	Increased glucose and triglycerides, reduced circulating fatty acids, reduced respiratory exchange ratio	PMID 22460952

Genetic Basis of Timing





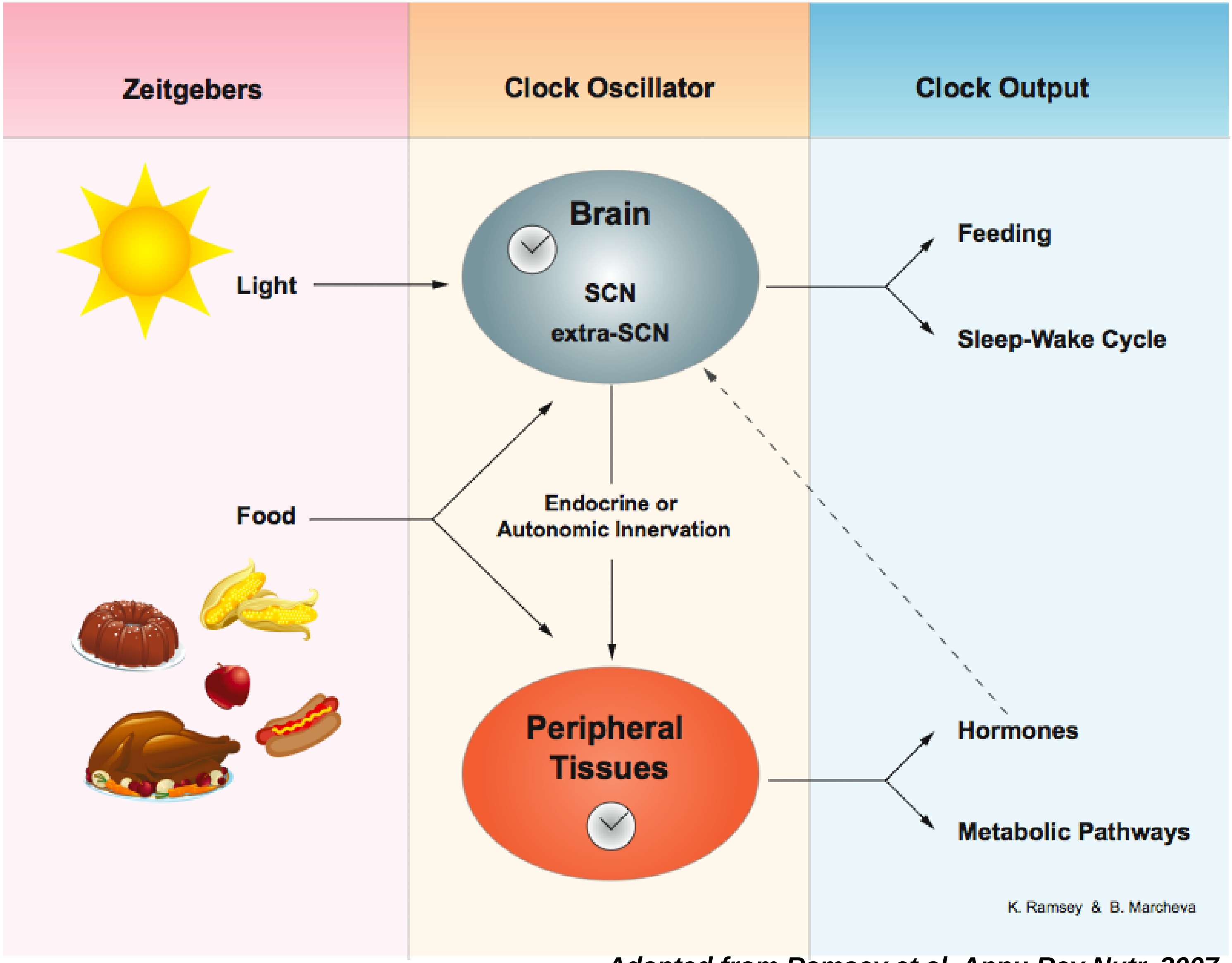
- Mouse Clock Mutant
  King et al., Cell, 1997

- Human *Per2* was discovered in people with <u>F</u>amilial <u>A</u>dvance <u>S</u>leep <u>P</u>hase <u>S</u>yndrome
  Toh et al., Science, 2001

Circadian Gene Polymorphisms and Metabolic Phenotypes (Human Genome-Wide Association Studies)

Polymorphisms	Metabolic Association	Reference
CLOCK	Hypertension, obesity, metabolic syndrome, non-alcoholic fatty liver disease, high plasma ghrelin, short sleep duration, altered eating behaviors, higher total energy intake, decreased compliance with prescribed diet plans, resistance to weight loss	PMID: 17696255, 18541547, 20653450, 20497782, 9846548, 19888304
BMAL1	Hypertension and type 2 diabetes	PMID: 17728404
CRY2	Altered fasting glucose concentrations	PMID: 20081858
PER2	Hyperglycemia, abdominal obesity, unhealthy feeding behavior, waist circumference and cholesterol levels	PMID: 19470168, 20205566, 20497782, 17653067
NAMPT1	Protection from obesity	PMID: 19300429
PER2/PER3/CLOCK/BMAL1	Morning or evening activity preference	PMID: 21637568
MTNR1A or MTNR1B	High fasting glucose levels, impaired insulin secretion, increased risk of type 2 diabetes, insulin resistance and susceptibility to poly cystic ovarian syndrome	PMID: 12957828, 21474908, 1470412, 21112029, 19241057,19937311, 20628598, 21658282, 22233651, 21474908, 19060908, 19088850

IV. Circadian Regulation of Metabolism



Adapted from Ramsey et al, Annu Rev Nutr, 2007

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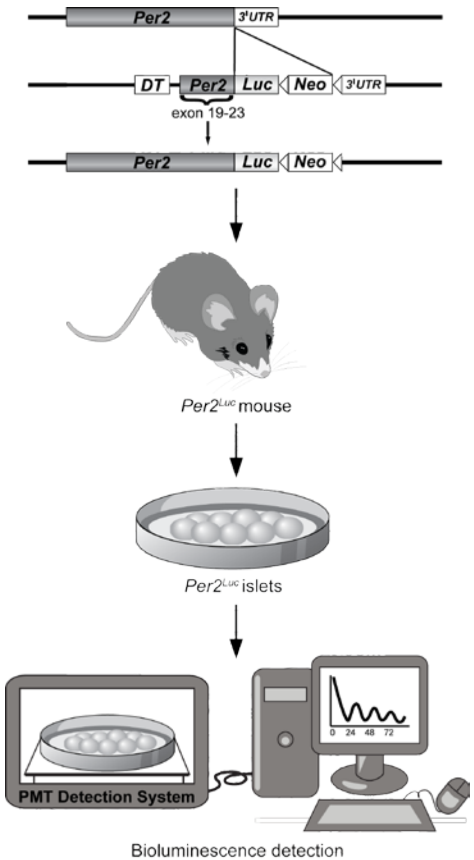
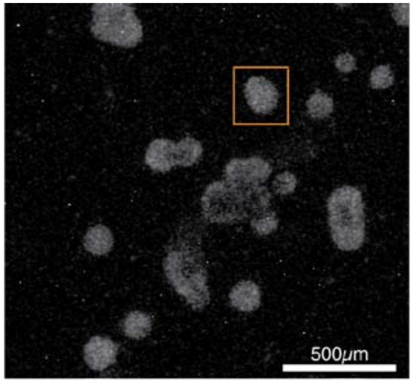
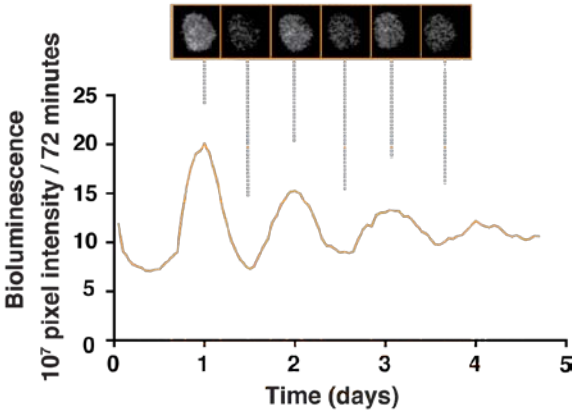
IV a. Glucose metabolism and insulin secretion:
Identification of Circadian Gene Oscillation in Pancreatic Islets

Marcheva et al., *Nature*, 2010





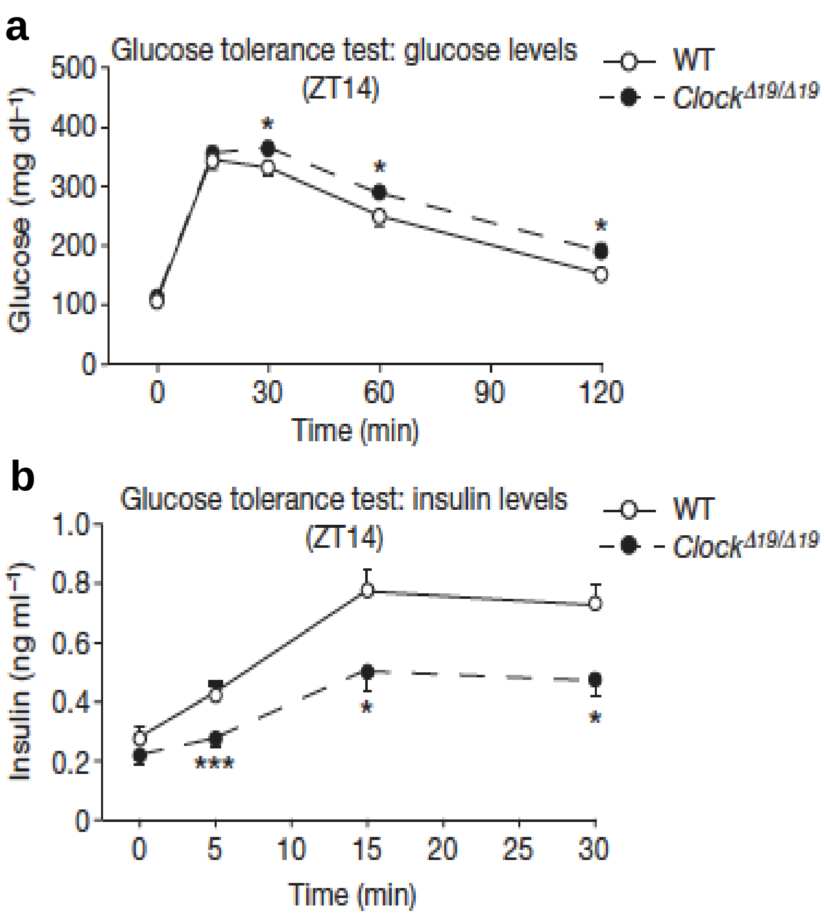


- Circadian clock is expressed autonomously within the pancreatic islet

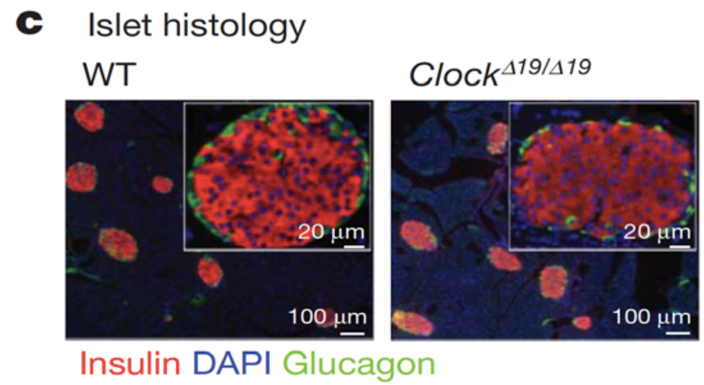
Development of Age-Dependent Diabetes in *Clock* Mutant Mice

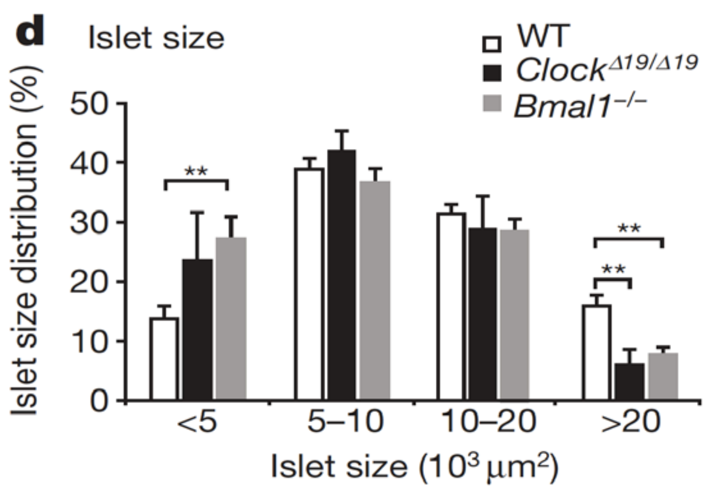
Marcheva et al., *Nature,* 2010

- Impaired glucose tolerance



- Reduced islet size, proliferation, and insulin release

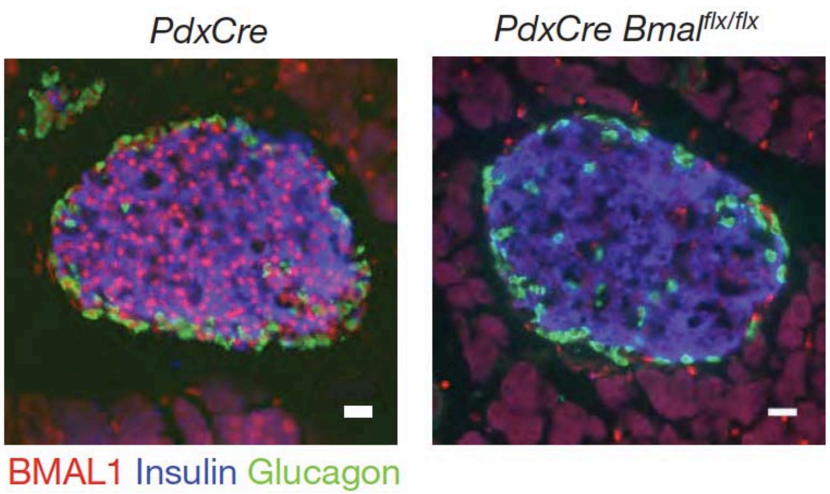




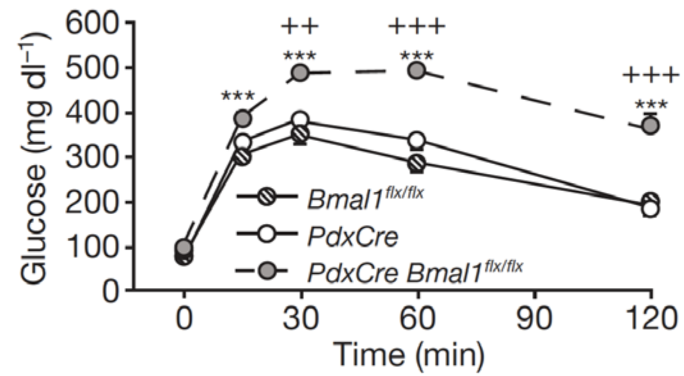
Multiple circadian genes impact the capacity of the pancreatic islets to respond to glucose

Marcheva et al., *Nature*, 2010

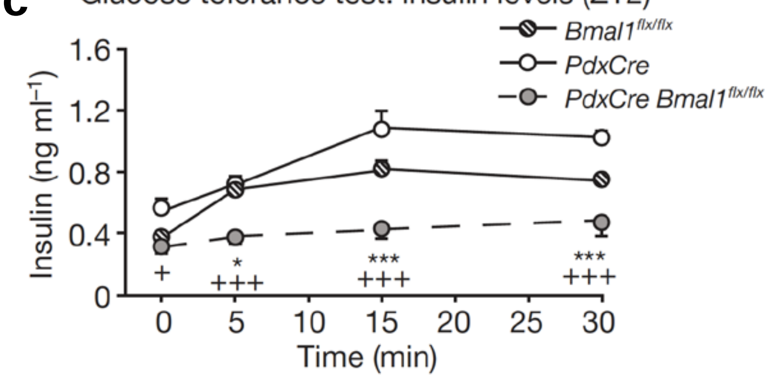
a Pancreas-specific *Bmal1* knockout: islet staining



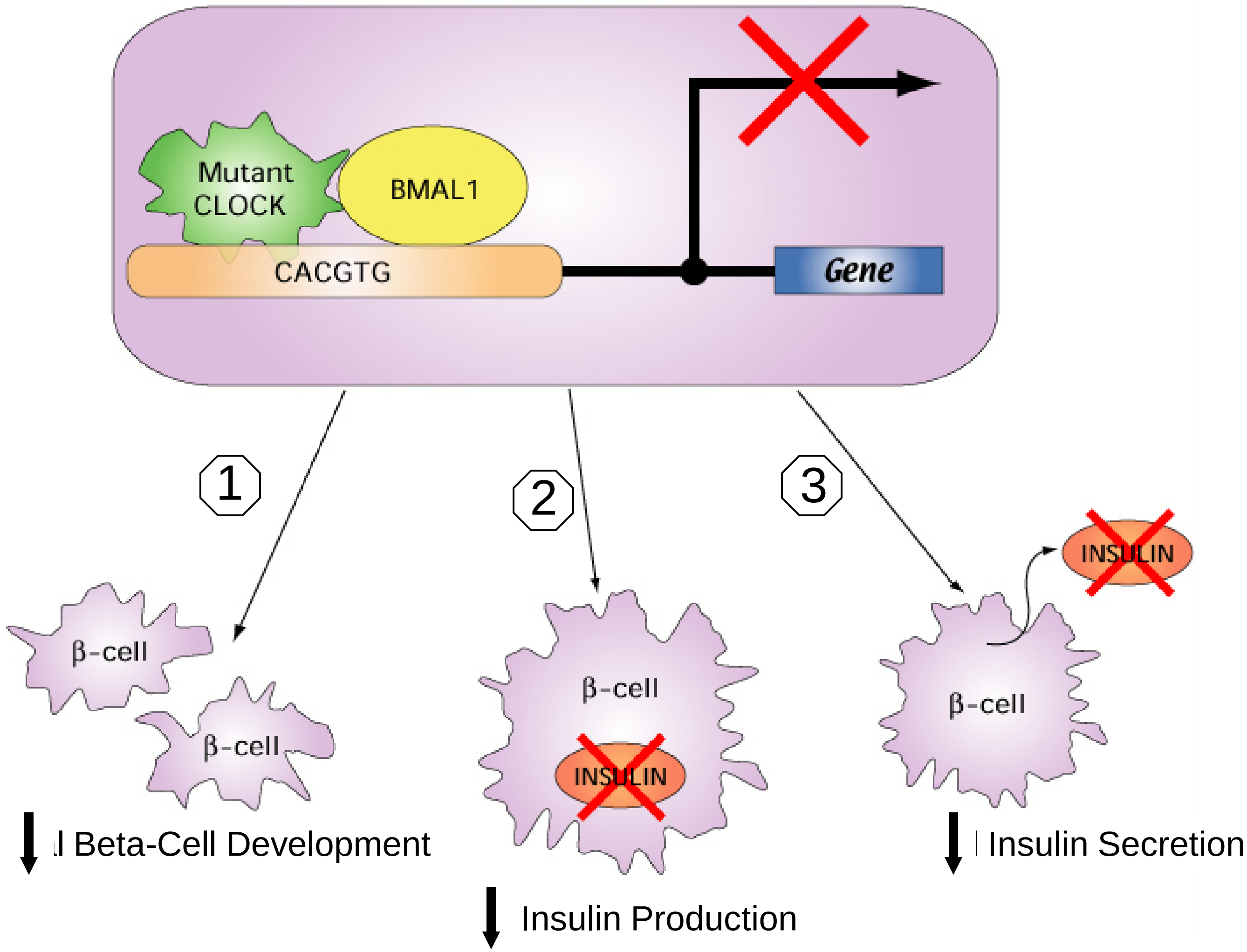
b Glucose tolerance test: glucose levels (ZT2)



c Glucose tolerance test: insulin levels (ZT2)

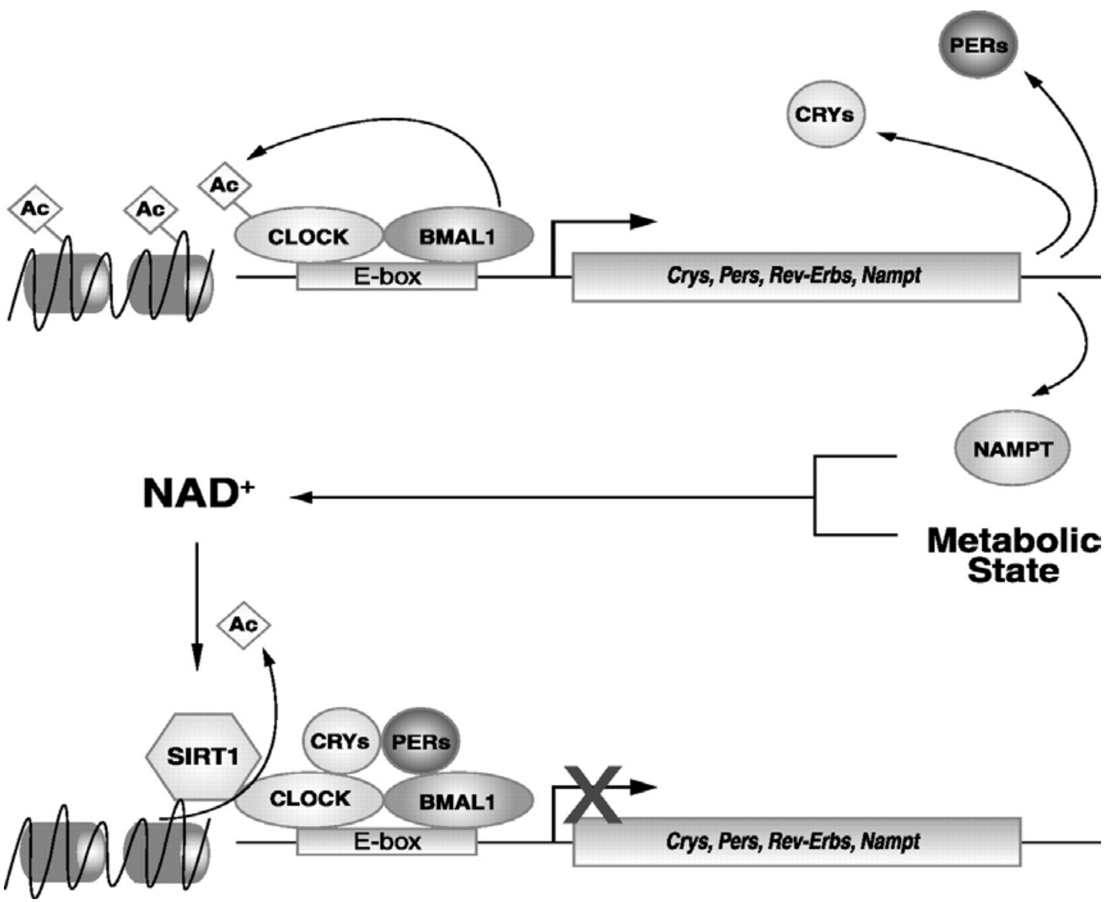


Potential Sites for Clock Gene Action in Glucose Stimulated Insulin Secretion



IV b. Molecular Clock Control of SIRT1 and NAD

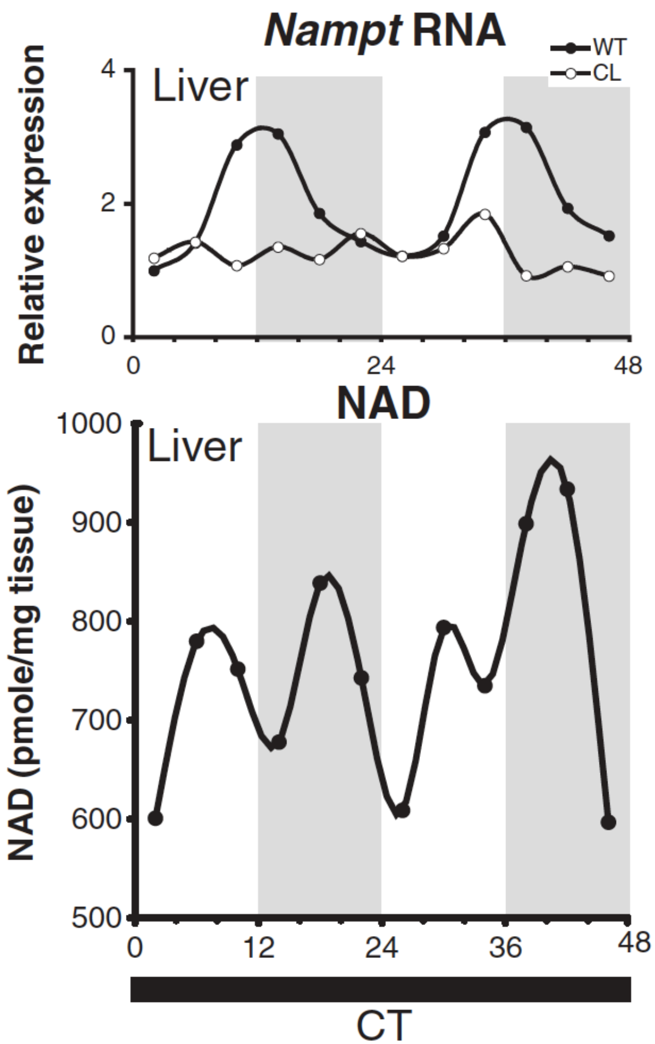
Ramsy et al., *Science*, 2009

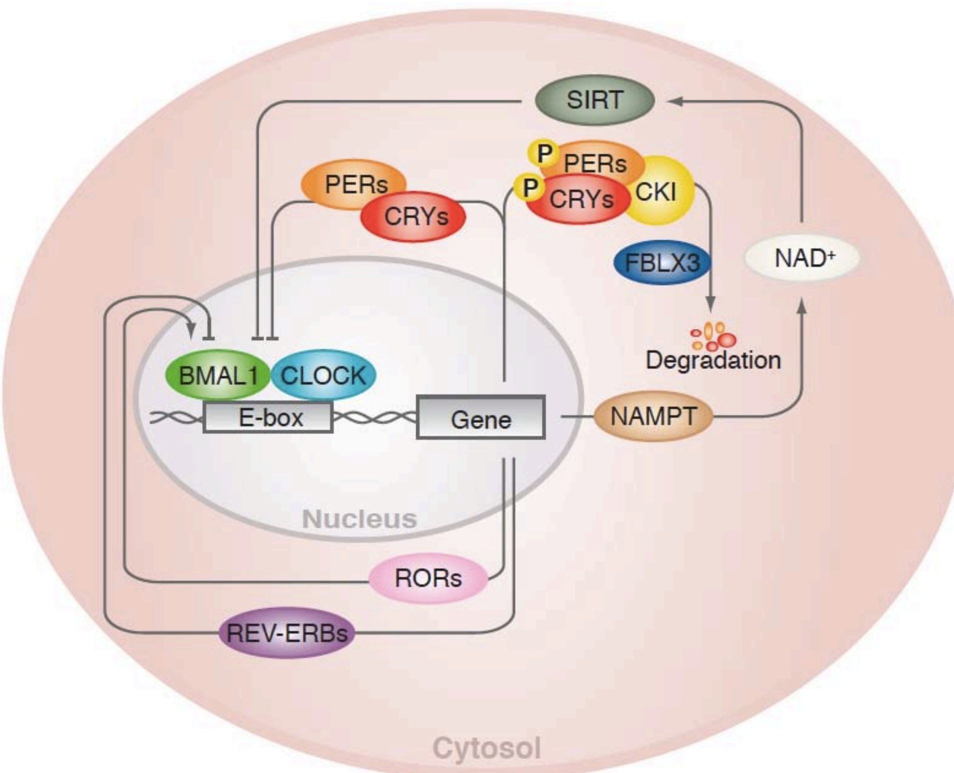


Marcheva B et al. J Appl Physiol 2009;107:1638-1646

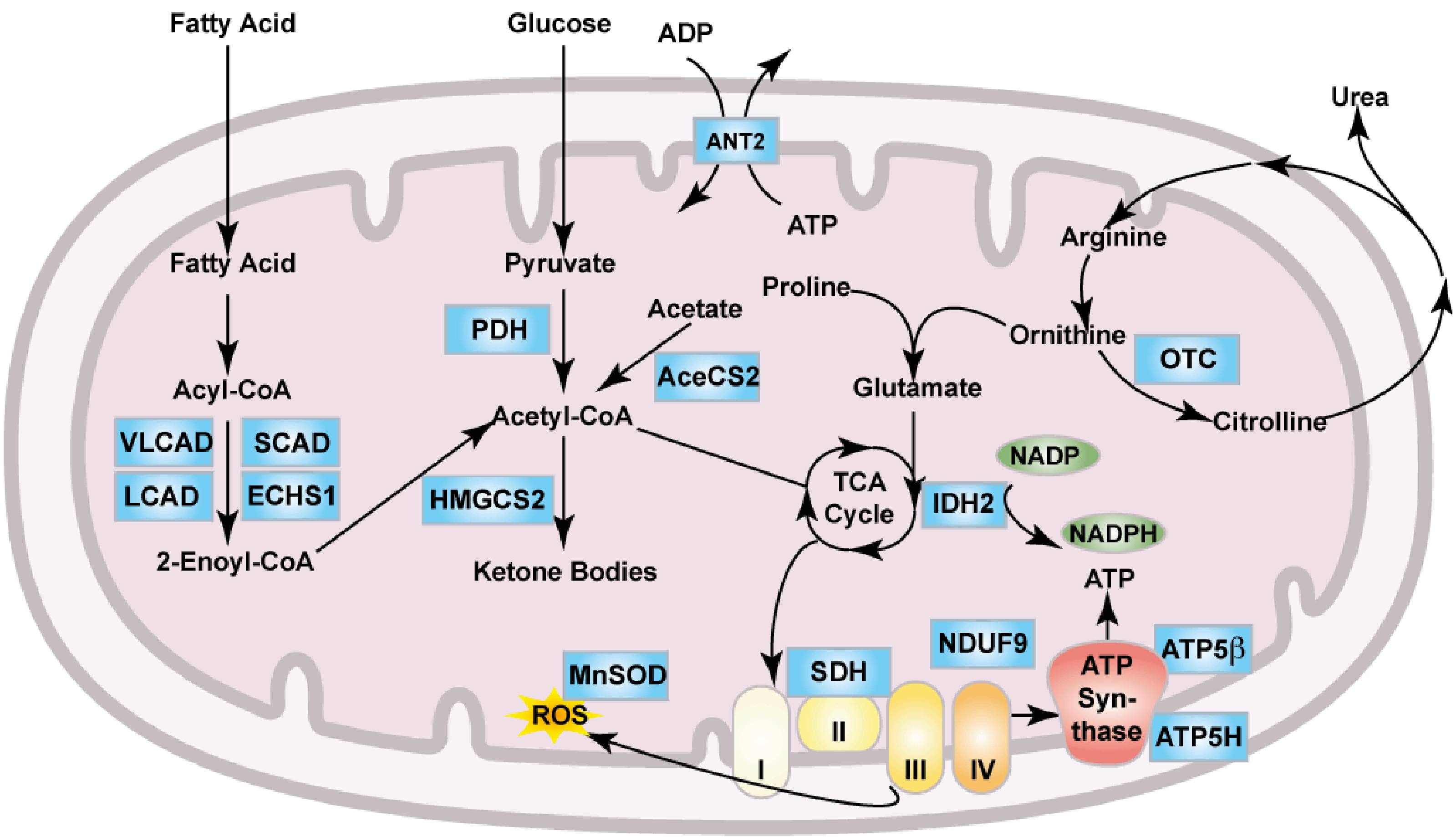
Circadian Oscillation of Nampt & NAD in Constant Darkness in WT and Clock mutant Mice

Ramsy et al., *Science*, 2009

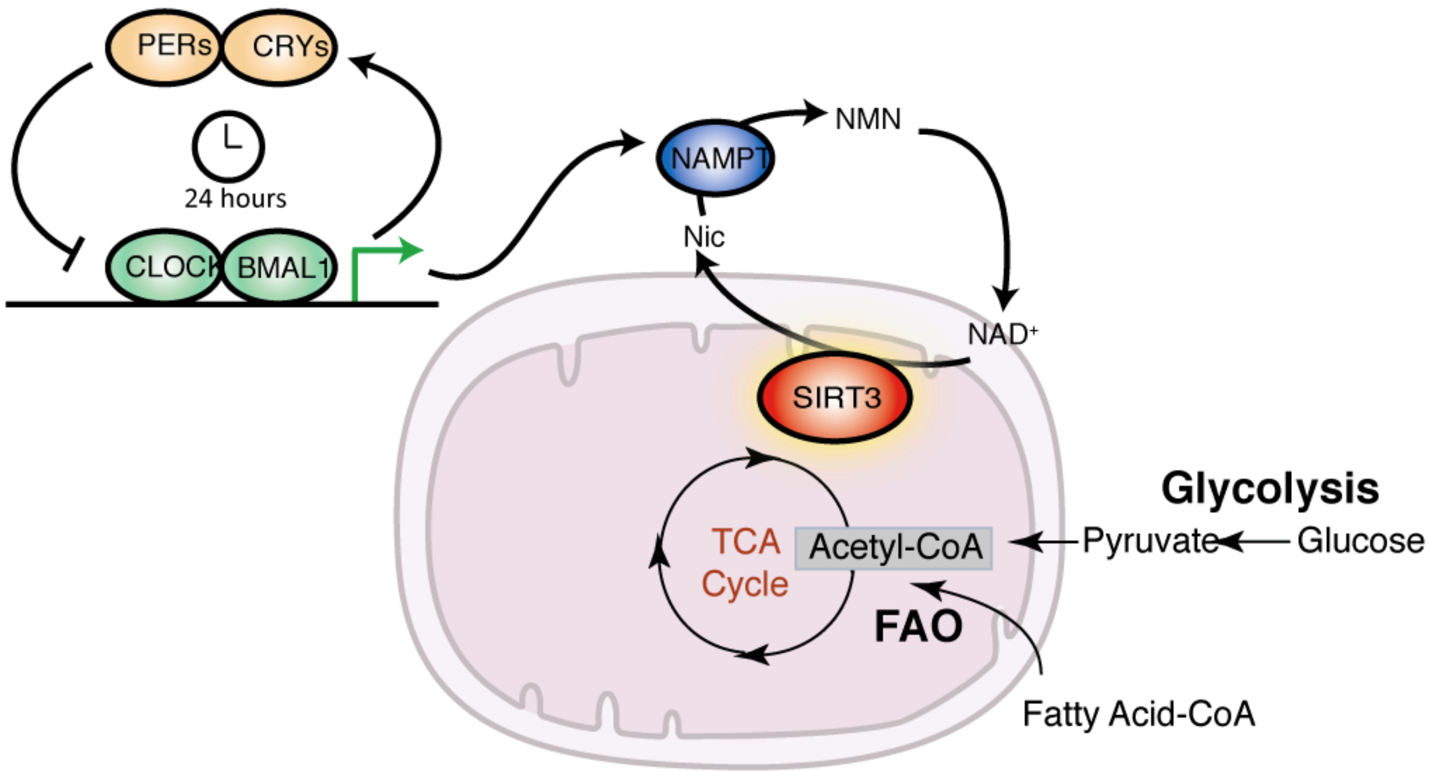


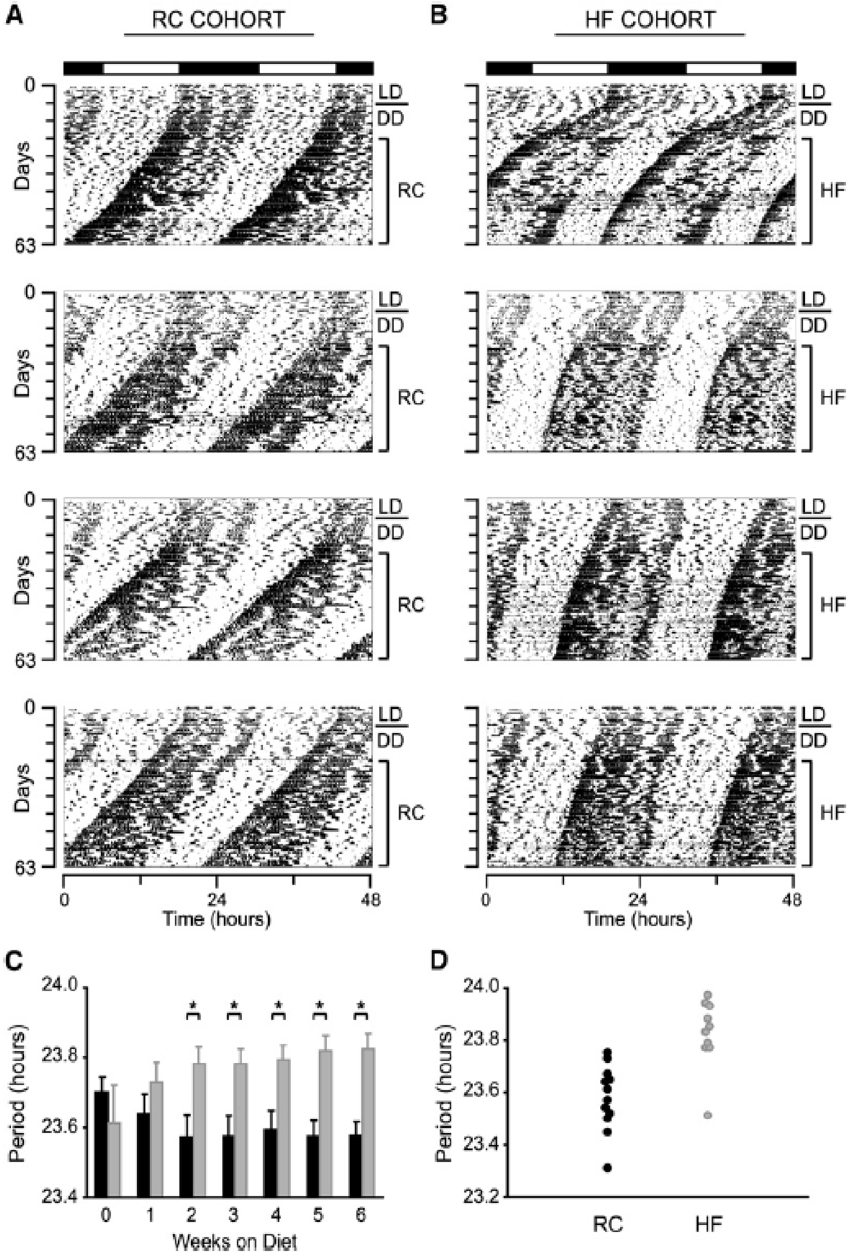


SIRT3 regulates mitochondrial oxidative function



Does the circadian clock regulate mitochondrial oxidative metabolism through rhythms of NAD+-driven SIRT3 activity?

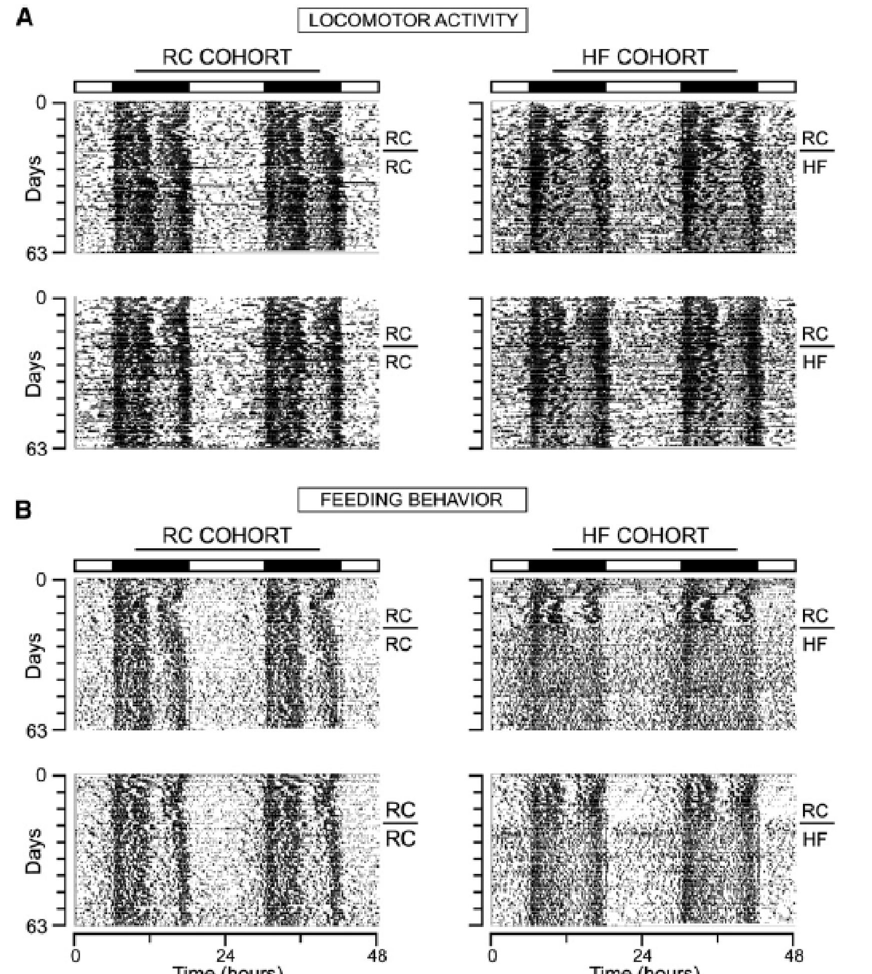




High-Fat Diet Disrupts Behavioral and Molecular Circadian Rhythms in Mice

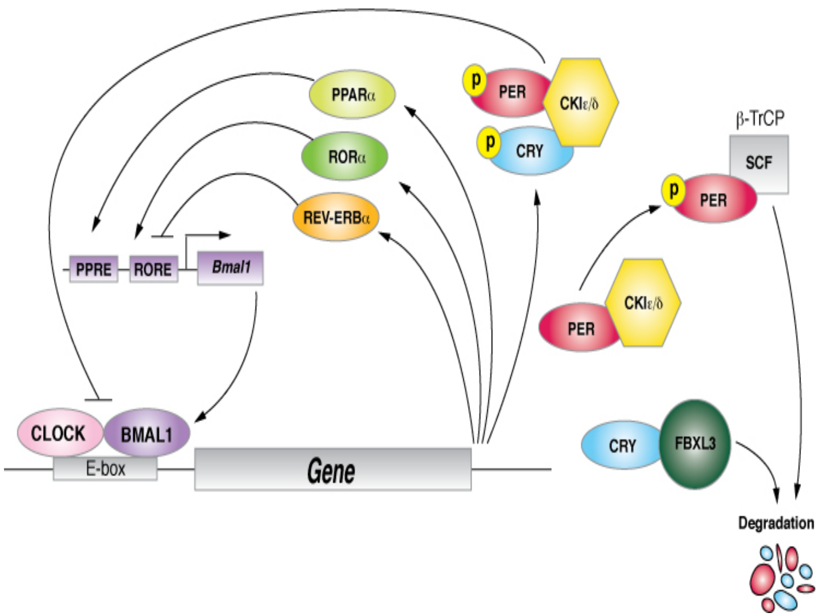
Cell Metabolism
(2007)

Akira Kohsaka,[1,4] Aaron D. Laposky,[1,2] Kathryn Moynihan Ramsey,[1,3,4] Carmela Estrada,[1] Corinne Joshu,[1] Yumiko Kobayashi,[4] Fred W. Turek,[1,2] and Joseph Bass[1,2,3,4,*]

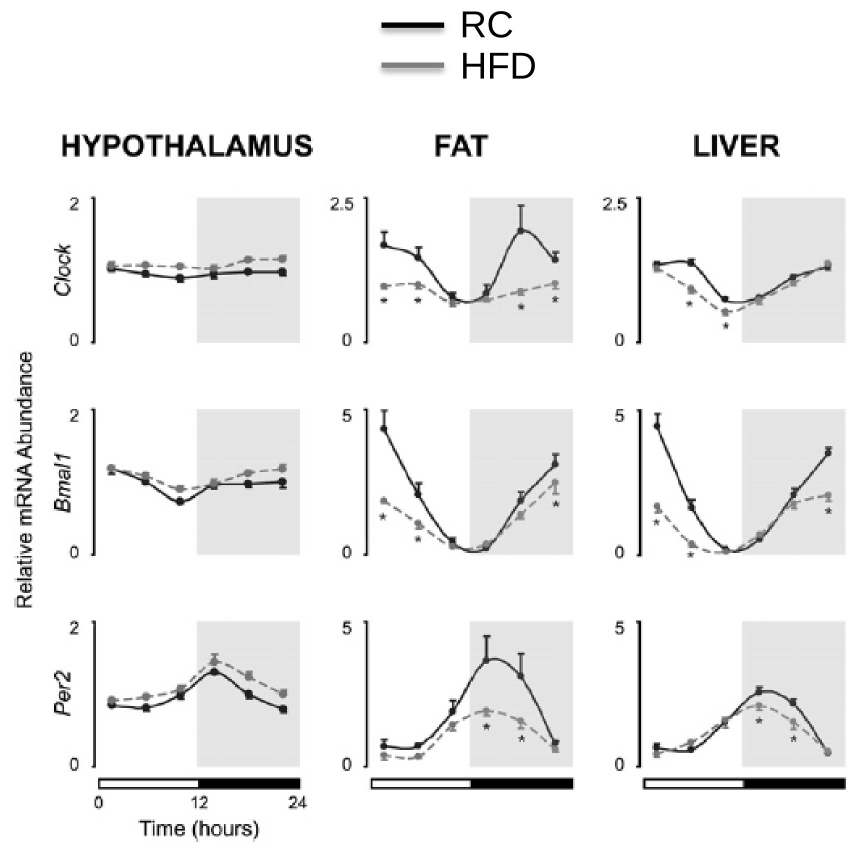


IV c. High-fat diet affects behavioral rhythms and attenuates clock gene expressions in metabolic tissues

Mammalian circadian clock



Adapted from Marcheva et al, J Appl Phys, 2009



Kohsaka et al. (2007)

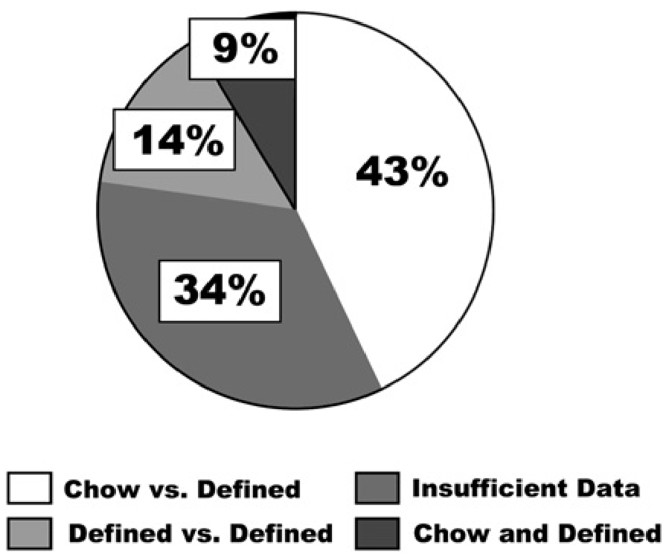
Question:
Are these disruptions of behavior due to the fat content of the diet?

Cell Metabolism
Correspondence

Comparisons of Diets Used in Animal Models of High-Fat Feeding

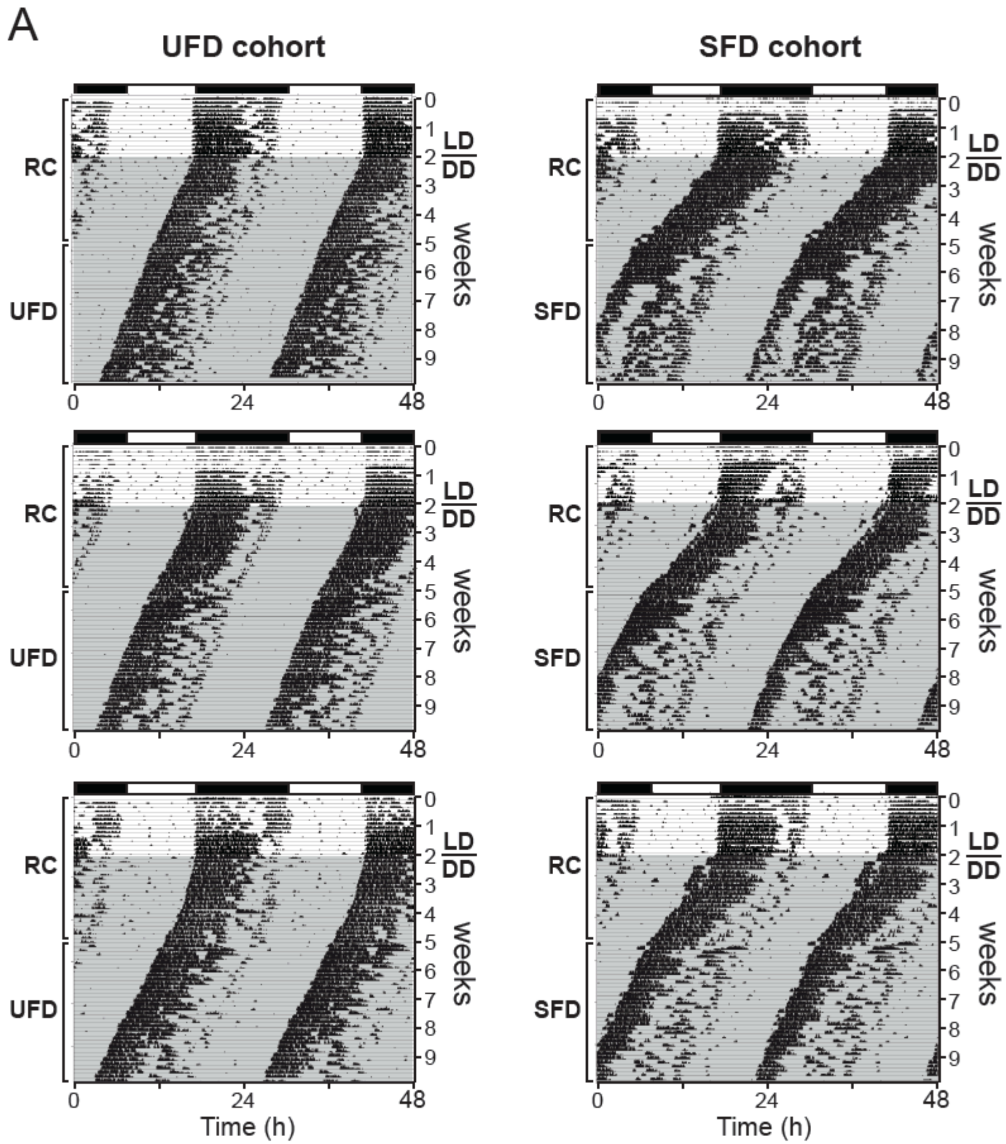
Craig H. Warden, and Janis S. Fisler
Cell Metabolism (2008)

"Many papers using animal models draw conclusions about dietary effects from comparison of natural-ingredient chow with defined diets, despite marked difference in micro and macronutrient content."

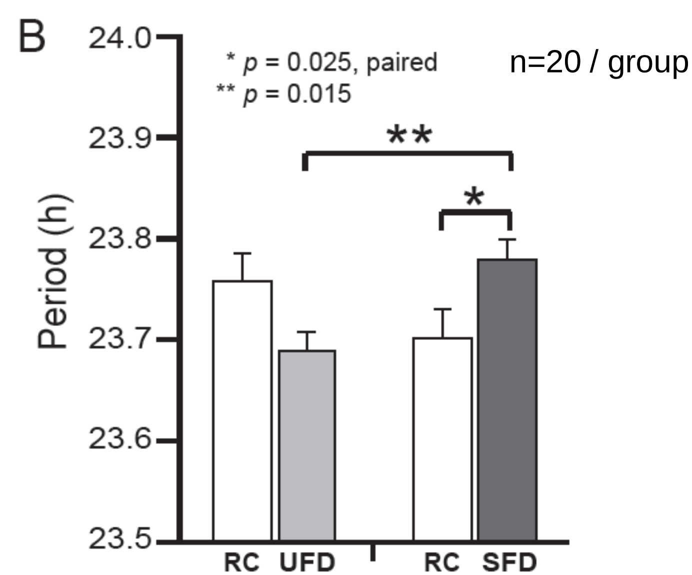


Diet Comparison in the Recent Research Paper

Does fatty acid composition of diet have differential effects on circadian period? UFD vs. SFD

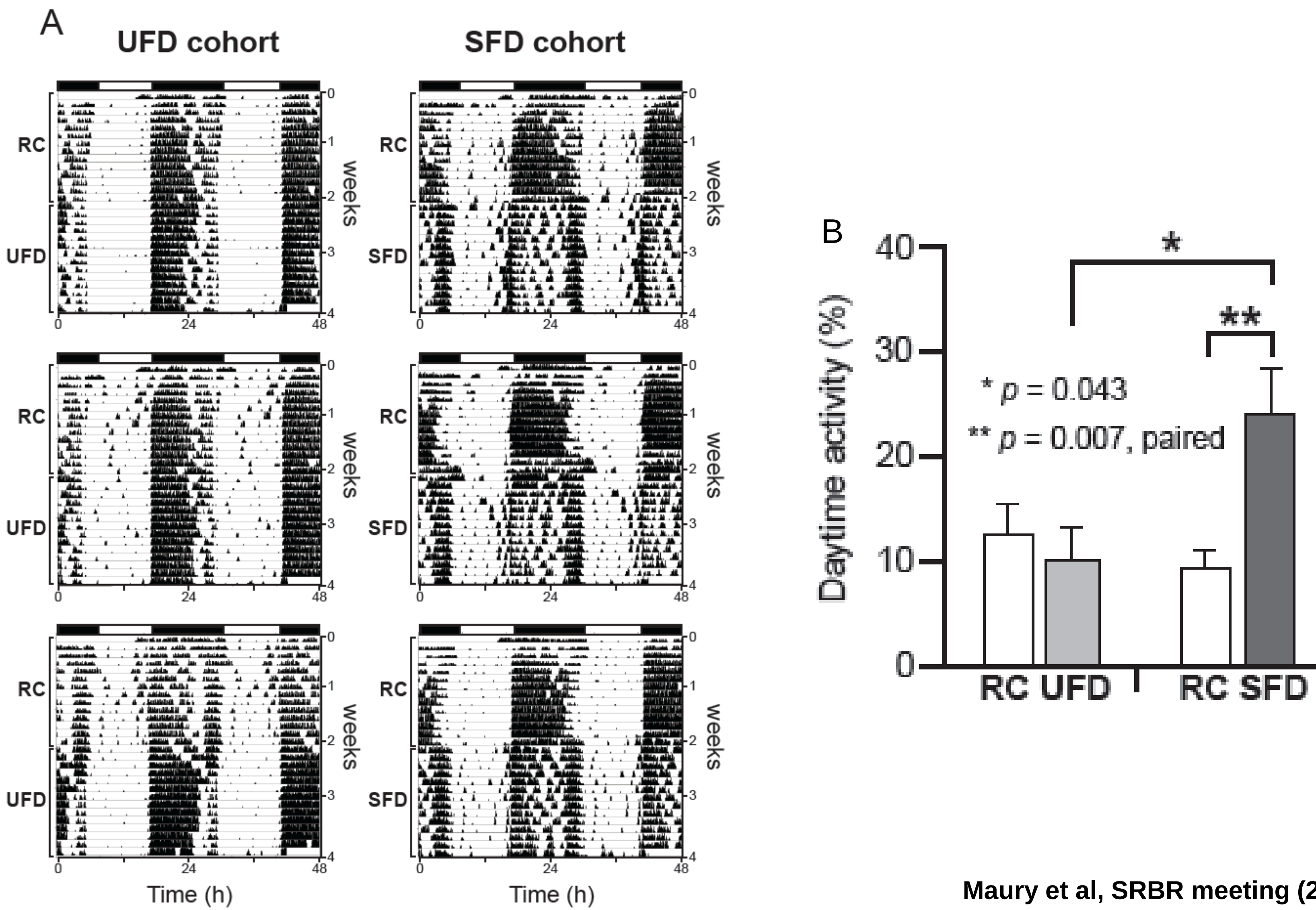


Kcal (%)	RC	UFD	SFD
Protein	27	20	20
Carbohydrate	57	35	35
Fat	16	45	45
Saturated fatty acids (C4:0, C6:0, C8:0, C10:0,C12:0, C14:0; C16:0; C18:0, C20)		6.4	26.3
Monounsaturated fatty acids (C14:1, C16:1, C18:1, C20:1)		29.8	13.5
Polyunsaturated fatty acids (C18:2, C18:3)		8.8	5.2



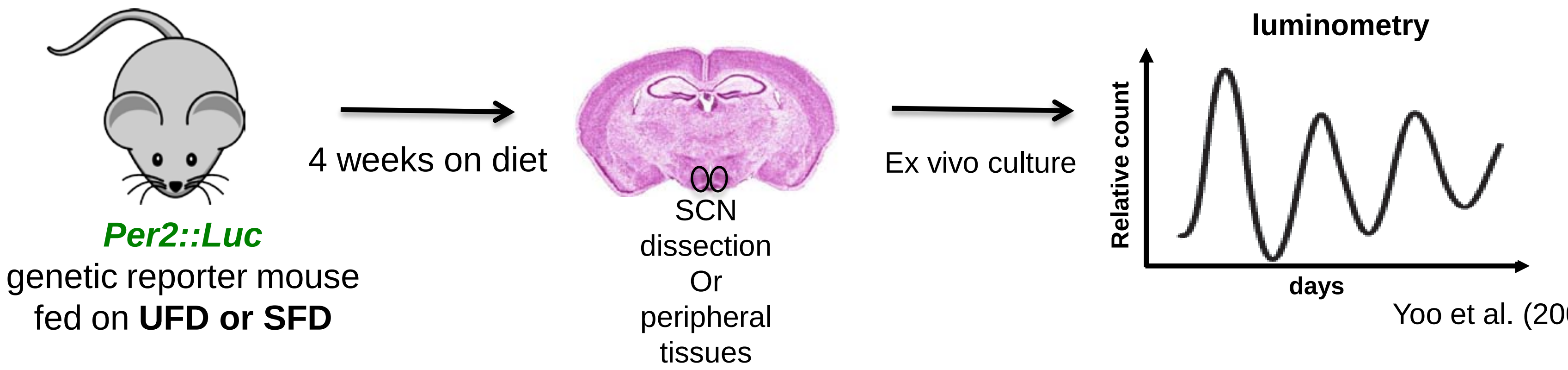
Maury et al, SRBR meeting (2012)

Differential effects of UFD and SFD on daytime activity



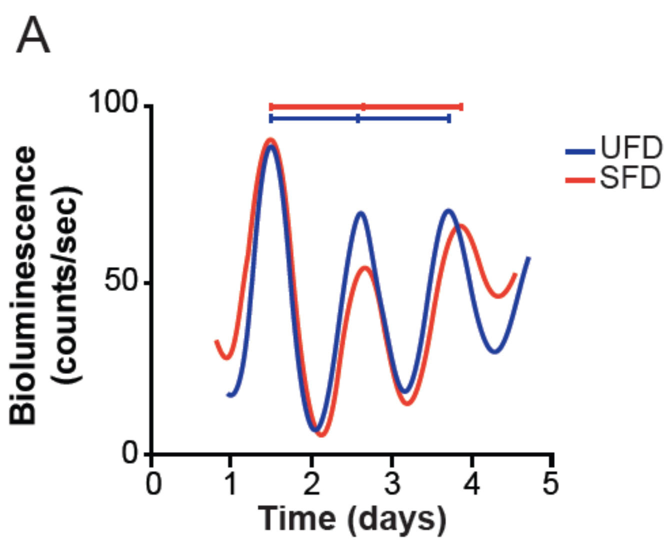
Maury et al, SRBR meeting (2012)

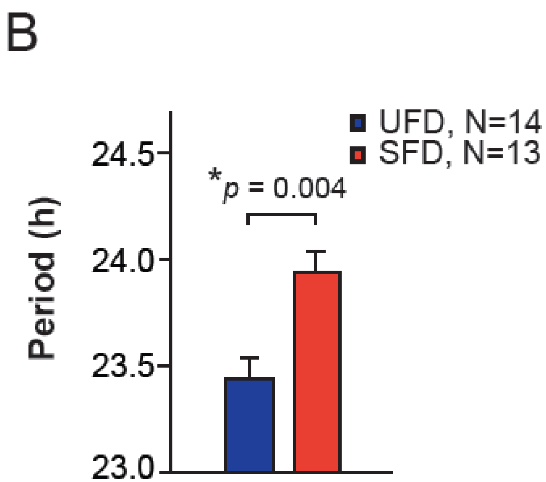
Fatty acid composition in diet affects properties of cell autonomous circadian oscillator



Yoo et al. (2004)

Diets enriched in saturated fatty acids *lengthens* behavioral rhythm and molecular clock in SCN.

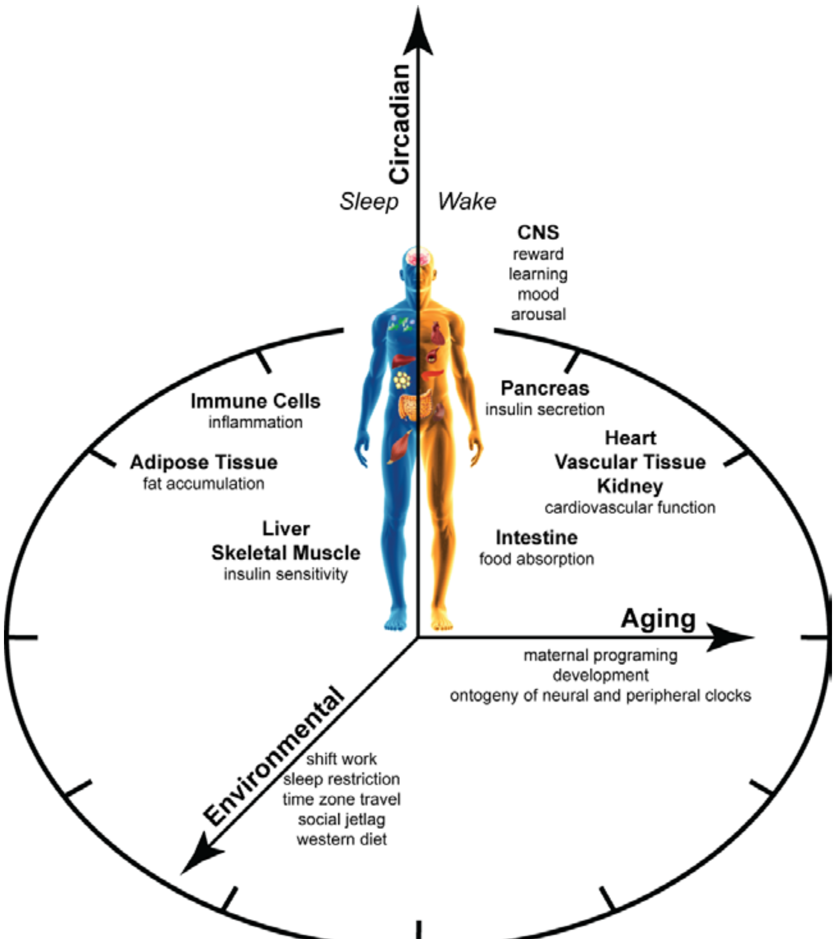




Maury et al, SRBR meeting (2012)

Acknowledgement

Environment factors contributing to circadian misalignment



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